BRIEFING PACKAGE

Division of Special Pathogen and Transplant Products
Office of Antimicrobial Products
Center for Drug Evaluation and Research, FDA

BLA 125349

RAXIBACUMAB

APPLICANT: HUMAN GENOME SCIENCES, INC.

ANTI-INFECTIVE DRUGS ADVISORY COMMITTEE MEETING

OCTOBER 27, 2009

PROPOSED INDICATION:
TREATMENT OF INHALATIONAL ANTHRAX

Proposed Dose:
One dose of raxibacumab 40 mg/kg IV over 2 hours
following diphenhydramine pre-treatment

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1. Introduction

In the fall of 2001, following dissemination of anthrax spores through the mail, eleven people developed inhalational anthrax, were treated with antimicrobial therapy, and 6/11 (55%) survived. This response rate exceeded the rate observed in cases of inhalational anthrax historically (4-11%),[1] and the improvement in survival was generally attributed to rapid administration of antimicrobial therapy and advances in supportive care. However, despite the best available interventions (multiple antimicrobials, pleural fluid drainage, mechanical ventilation, volume expansion, etc.), the mortality rate in patients that presented with inhalational anthrax during 2001 US attack was 45%.

Inhalational anthrax is caused by the Gram-positive bacterium, *Bacillus anthracis*, and antimicrobial treatment is directed at eradicating the bacterium. Antimicrobials, however, have no activity against the toxins produced by *B. anthracis*, which include lethal toxin (LT) and edema toxin (ET). These toxins are formed when *B. anthracis* elaborates the components needed to form these toxins: protective antigen (PA), lethal factor (LF) and edema factor (EF).

Therefore, Human Genome Sciences, Inc. (HGS) undertook the development of raxibacumab, a recombinant, fully human, $IgG_1\lambda$ monoclonal antibody directed at the PA of *B. anthracis*, as an addition to the available treatment armamentarium for patients with inhalational anthrax.

The proposed indication is the treatment of inhalational anthrax and the proposed treatment regimen of raxibacumab is 40 mg/kg administered as a single 2 hour IV infusion. Because of allergic reactions observed during the raxibacumab development program, pretreatment with diphenhydramine is recommended.

The development program included studies showing that raxibacumab binds PA with high affinity and inhibits PA binding to anthrax toxin receptor (ATR) on host cells, thereby protecting the cells from anthrax toxin-mediated injury. Proof-of-concept studies with raxibacumab demonstrated a survival advantage in the rat lethal toxin infusion model and in several pre-exposure and post-exposure prophylaxis animal model studies. The raxibacumab development program also included identification and characterization of the natural history of disease in animal models of anthrax disease (New Zealand White rabbits and Cynomologus monkeys), and these animal models were used to evaluate the efficacy of raxibacumab in the treatment of inhalational anthrax. Four key animal studies were conducted. These included two studies of raxibacumab monotherapy compared to placebo in the treatment of inhalational anthrax (rabbits and monkeys) and two studies of raxibacumab plus antimicrobials (levofloxacin in rabbits and ciprofloxacin in monkeys) in the treatment of inhalational anthrax. A summary of these studies is provided in Section 5 of this document. Clinical pharmacology on the pharmacokinetic characteristics of raxibacumab in humans, monkeys, and rabbits are summarized in Section 6 and include a comparison of exposures in humans and animal species.

[1] Inglesby TV et al, Anthrax as a biological weapon, 2002: updated recommendations for management. JAMA. 2002 May 1;287(17):2236-52

Efficacy studies were conducted in animal models of infection because naturally-occurring inhalational anthrax infection in humans is rare to nonexistent and intentional exposure of healthy human volunteers to aerosolized *B. anthracis* spores for research purposes is unethical. Information on the Animal Rule, which allows the FDA to rely on efficacy based on animal studies, is discussed in Section 2.

The safety of raxibacumab in normal volunteers and preclinical results of raxibacumab testing are provided in Section 7. These studies demonstrated that raxibacumab was associated with the development of allergic reactions (primarily rash); therefore, subsequent studies in human subjects and monkey efficacy studies included diphenhydramine pre-treatment. Immunogenicity was evaluated for this intravenous product, and the results suggest a low risk for immunogenicity.

1.1 Bacillus anthracis and Anthrax Disease

1.1.1 Background

Bacillus anthracis is considered a CDC Category A potential agent for bioterrorism. *B. anthracis* spores are environmentally hardy, and thus, readily bioweaponized. World Health Organization estimates that intentional release of 50 kg of *B. anthracis* over an urban population of 5 million would sicken 250,000 and kill 100,000. A US Congressional Office of Technology assessment analysis estimates that between 130,000 and 3 million deaths would follow the release of 100 kg of *B. anthracis*, a lethality matching that of a hydrogen bomb.

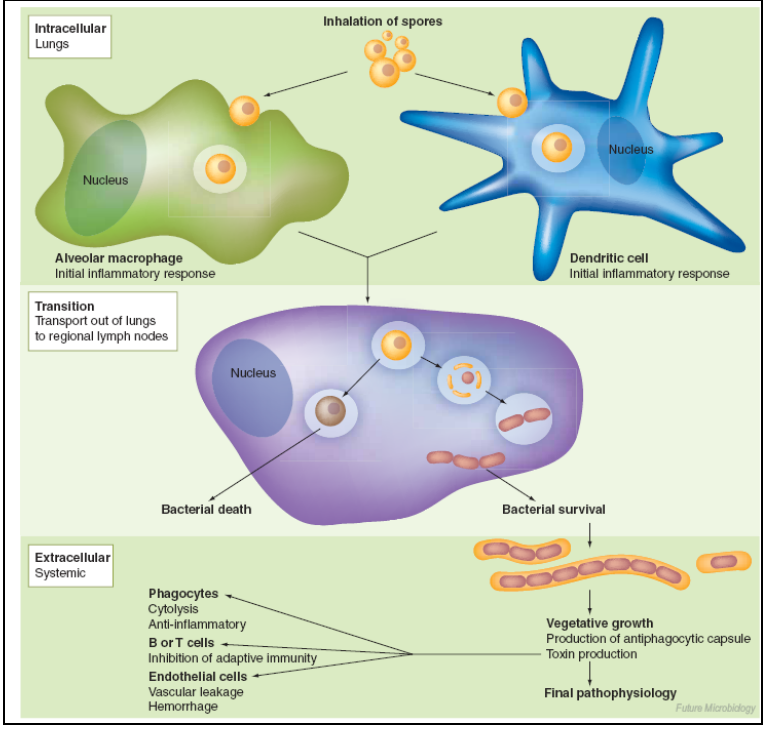
1.1.2 *Bacillus anthracis*

B. anthracis is a Gram-positive, toxin-producing, encapsulated, spore-forming, facultative anaerobic bacillus that causes three forms of anthrax depending on the route of exposure: cutaneous, gastrointestinal (GI), and inhalational. Inhalational anthrax disease results from entry of the *B. anthracis* spores via the respiratory tract and deposition in the lung. In the alveolar spaces, macrophages phagocytize the spores and then migrate to regional lymph nodes. The organisms proliferate in the lymph nodes, rather than as a primary focus in the lungs (Figure 1)[2]. The appearance of organisms in the lymphatics draining the lungs and the establishment of infection in the intrathoracic lymph nodes always precedes the development of bacteremia after aerosol exposure. As the phagocytic capacity of the lymph node is overwhelmed, vegetative organisms pass through efferent lymphatics, infect successive nodes, and ultimately enter the blood stream through the thoracic duct.

In the macrophages, the spores germinate within phagosomes and produce anthrax toxin, which is comprised of three protein components: lethal factor (LF), edema factor (EF), and protective antigen (PA). Individually, these components are harmless; however, they combine to form noxious toxins. In infection, all three anthrax toxin components (i.e., PA, LF, and EF) would be present.

[2] Passalacqua, KD and Bergman, NH, *Bacillus anthracis*: interactions with the host and establishment of inhalational anthrax. Future Microbiology (2006) 1(4): 397-415.

Figure 3.1-1. Diagrammatic Representation of Interactions between *B. anthracis* and the Host During Inhalational Anthrax[2]



1.1.3. Virulence Factors

The major virulence factors for *B. anthracis* are the capsule and anthrax toxins. The *B. anthracis* capsule enables the vegetative form of *B. anthracis* to avoid phagocytosis. All three components of anthrax toxin: PA, LF, and EF are present during established infection. A study has demonstrated that PA is present on the surface of spores, and human monoclonal antibody can bind the PA on the surface of spores.[3] PA is the receptor-binding component that allows intracellular entry of LF and EF. EF is a calmodulin-dependent adenylate cyclase that induces edema in various tissues. LF is a zinc metalloprotease that cleaves and inactivates mitogen-activated protein kinase kinases (MAPKKs), key signal transduction molecules required for effective host responses against bacterial pathogens as well as cellular functions. There has been experimental utility in examining the independent effects of EF and LF, each in combination with their shared receptor-binding component, PA. LT targets a variety of cell types, including immune cells (macrophages, dendritic cells, neutrophils and lymphocytes), leading to disruption of immune responses, and thereby facilitating infection. LT also has toxic effects on endothelial cells, leading to loss of barrier function, which is thought to be a major factor underlying the pathology induced by LT. It is notable that LT, despite its name, is not directly lethal to most cells in culture. Instead, it acts to disrupt a wide variety of cellular functions that require MAPKK signaling (e.g., cell cycling and cytokine production). Similarly, ET has wide-ranging effects through its enzymatic activity that results in

[3] Cote, C, Rossi, CA, Kang, AS, Morrow, PR, Lee, JS, and Welkos, SL. The detection of protective antigen (PA) associated with spores of *Bacillus anthracis* and the effects of anti-PA antibodies on spore germination and macrophage interactions. Microbial Pathogenesis (2005) 38: 209-225.

increased cellular cyclic AMP, a critical cellular signaling molecule. In addition to mediating edema, ET has immunomodulatory effects and perturbs endocrine function.[4] The secreted *B. anthracis* toxins are thought to be responsible for the morbidity and high mortality rates characteristic of anthrax infection despite appropriate antimicrobial therapy.

Monomeric PA is secreted as an 83 kDa protein that is cleaved by a host protease, such as furin, to remove an N-terminal 20 kDa fragment. There is some controversy as to whether this happens only on the cell surface after PA binds to the receptor or whether the cleavage can also occur before PA binds to the cellular receptor. In either case, seven 63 kDa fragments of PA then assemble into a heptamer ring on the cell surface leading to the formation of binding sites for up to three molecules of LF and/or EF. The toxin complex is internalized by endocytosis, a pore is formed in the acidic environment of the endosome, and LF and EF are extruded into, and exert their effects in, the cytosol.[5]

PA, LF, and EF are encoded by the pX01 plasmid. Another plasmid, pXO2, contains the genes for the synthesis of a poly-c-D-glutamic acid capsule. The expression of the genes encoding the capsule are under the control of two regulatory gene products, anthrax toxin activator (AtxA) and anthrax capsule activator (AcpA), that are also located on the pX01 and pXO2 plasmids. AtxA and AcpA respond to as yet undefined environmental cues.[6]

There are at least two cell receptors for PA, ANTXR1/tumor endothelial marker 8/TEM8 and ANTXR2/capillary morphogenesis gene 2/CMG2. At least one of these receptors is found on essentially all mammalian cells. PA binds to both receptors with high affinity and mediates toxicity through either receptor. Both receptors are Type 1 transmembrane proteins with an extracellular von Willebrand factor A domain (integrin inserted domain; VWA/I) that contains a metal ion-dependent adhesion site (MIDAS) that interacts with PA. The PA binding site is conserved between the two receptors with 60% identity within the VWA/I domain and 40% overall amino acid identity.[7]

1.1.4 Human Infection

B. anthracis is a bacterium found in nature and is historically associated with disease in the agricultural setting, and later, in industrial settings (ragpickers or woolsorters disease[8]). Disease can be acquired by the cutaneous, gastrointestinal or inhalational route of entries. Cutaneous anthrax is generally characterized by a local eschar and responds well to antimicrobial treatment. Gastrointestinal and inhalational anthrax are generally associated with bacteremia, toxemia, and even with antimicrobial treatment, are often fatal.

Natural disease was very rare in the 20th century, with the exception of two situations following aerosolized exposures. In 1979, accidental release of *B. anthracis* spores from a factory in

[4] Moayeri and Leppla, Cellular and systemic effects of anthrax lethal toxin and edema toxn. Mol Asp of Med, 2009, in-press, but on-line.
[5] Xu, L and Frucht, DM. Bacillus anthracis: a multi-faceted role for anthrax lethal toxin in thwarting host immune defenses. Internat. J. Biochem. Cell Biol (2007) 39: 20-4.
[6] Hirsh, DC and Biberstein, EL. Bacillus IN Hirsch, DC, MacLachlan, NJ, and Walker, RL (eds). Veterinary Microbiology. 2004. Blackwell Press, Ames, IA, USA.
[7] Banks, DJ, Ward, SC, and Bradley KA. New insights into the functions of anthrax toxin. 2006. Expert Rev. Mol. Med. 8 (7):1-18.
[8] Brachman PS. Inhalational anthrax. *Ann NY Acad Sci* 1980; 353:83-93.

Sverdlovsk, Russia, led to 66 deaths due to inhalational anthrax[9], and in 2001, *B. anthracis* was disseminated through the US mail resulting in 22 cases of anthrax, including 11 cases of cutaneous anthrax and 11 cases of inhalational anthrax. All patients with cutaneous anthrax responded to treatment. Mortality in the US inhalational anthrax cases was 45% (5/11).[10]

Early diagnosis of inhalational anthrax is difficult and requires a high index of suspicion. Prior to the 2001 attacks, clinical information was limited to a series of 18 cases reported in the 20th century and the limited data from Sverdlovsk. Inhalational anthrax had been described as a two-stage illness.

The disease has a typical incubation period of 1-6 days and begins with relatively mild, flu-like symptoms such as malaise, fatigue and slightly elevated temperature. Some patients complain of dyspnea, cough, vomiting, chills, weakness, abdominal pain, and chest pain. Signs of illness and laboratory studies are nonspecific. This stage of illness lasts from hours to a few days.
In some patients, a brief period of apparent recovery follows. Other patients progress directly to the second, fulminant stage of illness characterized by respiratory failure and shock. This second stage develops abruptly, with sudden fever, dyspnea, diaphoresis, and shock. Massive lymphadenopathy and expansion of the mediastinum lead to stridor in some cases. A chest radiograph most often shows a widened mediastinum consistent with lymphadenopathy. Up to half of patients develop hemorrhagic meningitis with concomitant meningismus, delirium, and obtundation. In this second stage, cyanosis and hypotension progress rapidly; death sometimes occurs within hours.

1.2 Currently Available Anthrax Therapies

1.2.1 Anthrax Treatment

The following antimicrobials in the tetracycline and penicillin class are approved for the treatment of anthrax due to *B. anthracis*:

> Tetracyclines: doxycycline, doxycycline calcium, doxycycline hyclate. Tetracycline, demeclocycline hydrochloride and minocycline hydrochloride are recommended in situations when penicillin is contraindicated
>
> Penicillins: penicillin G procaine, penicillin G potassium, and penicillin G sodium.

1.2.2 Post-Exposure Prophylaxis of Anthrax

Between 2000 and 2004, a number of antimicrobials were labeled for post-exposure prophylaxis of inhalational anthrax, based on the recognition that *B. anthracis* was a Category A bioterrorism agent

[9] Abramova FA et al. Pathology of inhalational anthrax in 42 cases from the Sverdlovsk outbreak in 1979. *Proc Natl Acad Sci USA* 1993; 90:2291-4.
[10] Jernigan JA, Stephens DS, Ashford DA, Omenaca C, Topiel MS, Galbraith M, et al. Bioterrorism-related inhalational anthrax: the first 10 cases reported in the United States. *Emerg Infect Dis* 2001;7:933–44. Barakat LA, Quentzel HL, Jernigan JA. Fatal inhalational anthrax in a 94-year-old Connecticut woman. *JAMA* 2002;287:863–8.

based on the CDC classification, and treatment would be needed in the event of intentional release of anthrax spores.

The first antimicrobial approved for inhalational anthrax (post-exposure) was ciprofloxacin in August, 2000. Approval was under 21 CFR 314.510, Subpart H of the regulations for accelerated approval[11] and was based on pharmacokinetic data as a surrogate likely to predict clinical benefit in humans. Specifically, the human exposures with ciprofloxacin 500 mg PO (400 mg IV) regimen matched the ciprofloxacin exposures achieved in Rhesus monkeys that proved efficacious in the Rhesus monkey model of post-exposure prophylaxis.[12]

The same Rhesus monkey study that was used to evaluate ciprofloxacin efficacy also included separate doxycycline and penicillin G procaine treatment arms; each of which similarly demonstrated a survival advantage over placebo in post-exposure prophylaxis. FDA determined that the language in the labeling of antimicrobial products containing doxycycline, doxycycline calcium, doxycycline hyclate, and penicillin G procaine is intended to, and does, cover all forms of anthrax, including inhalational anthrax (post-exposure): "To reduce the incidence or progression of disease following exposure to aerosolized *Bacillus anthracis*."[13] Labeling of these products was, therefore, amended to provide for a dosing regimen for inhalational anthrax (post-exposure).

Subsequently, a monkey study of post-exposure prophylaxis of inhalational anthrax was conducted with levofloxacin, and supported approval of this indication in adults (November 24, 2004) and pediatric patients (May 5, 2008). Safety data were available for up to 28 days in adults and 14 days in pediatric patients, and this information was reflected in labeling. As with ciprofloxacin, levofloxacin was approved under the subpart H regulations for accelerated approval.

1.2.3 CDC Recommendations on Anthrax Management[14]

Following the anthrax attacks of 2001, the CDC recommended the use of two or three antimicrobials in combination in persons with inhalational anthrax based on susceptibility testing with epidemic strains. Limited early information suggested that patients treated intravenously with two or more antimicrobials active against *B. anthracis* had a greater chance of survival.

1.3 Unmet Medical Need

Anthrax disease is associated with three principle virulence factors of *B. anthracis*: its antiphagocytic capsule and two protein exotoxins (lethal and edema toxins). Antimicrobial treatment results in killing and eradication of the susceptible bacteria; however, antimicrobials have no activity against the toxins as evident by high mortality rate (45%) despite the best available treatments in inhalational anthrax cases during 2001 US attack.

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[11] 21 CFR 314.510 (Subpart H – Accelerated Approval of New Drugs for Life-Threatening Illnesses)

[12] Friedlander AM, Welkos SL, Pitt MLM, et al. Postexposure prophylaxis against inhalation anthrax. J Infect Dis 1993;167:1239-42.

[13] Federal Register / Vol. 66, No. 213 / Friday, November 2, 2001 / Notices

[14] Update: Investigation of Bioterrorism-Related Anthrax and Interim Guidelines for Exposure Management and Antimicrobial Therapy, October 2001 *MMWR. 2001;50(42):909-19*

Raxibacumab, a fully humanized monoclonal antibody with specific high affinity to PA, could broaden the available armamentarium for the treatment of systemic anthrax.

There is also a growing body of evidence that a bioengineered, drug-resistant anthrax strain could be a concern in the intentional release setting. In such an event, raxibacumab might be the only effective treatment.

Finally, raxibacumab could also be used as an alternative therapy when antimicrobials or vaccines are contraindicated (see CONTRAINDICATIONS and WARNINGS sections in the prescribing information for Cipro®, Levaquin®, Vibramycin®, and BioThrax®), or for subjects who cannot tolerate these therapeutic products.

2. Regulatory Background

2.1 IND Submission, Fast Track, and Orphan Designation

The development of raxibacumab began with the submission of the IND for raxibacumab (PA mAb) on May 22, 2003 and a Phase 1 protocol to evaluate the safety, tolerability, and PK of raxibacumab in healthy volunteers (Protocol PAM-NH-01).

During the course of development, HGS requested Fast Track designation for raxibacumab for the treatment of inhalation anthrax that was granted by FDA on August 15, 2003 for the investigation of raxibacumab for post-exposure prophylaxis and adjunctive therapy of inhalation anthrax disease, and for lessening the severity of inhalation anthrax disease, including disease caused by antibiotic resistant organisms.

Raxibacumab was also granted orphan designation for the treatment of subjects with inhalation anthrax on November 12, 2003.

2.2 Completed Studies List for Biologic Licensing Application (BLA)

For a complete list of the preclinical and clinical studies conducted to evaluate raxibacumab, see Appendix 3 at the end of this document. The BLA was submitted May 14, 2009.

2.3 Animal Rule (New Drugs and Biologics)[15]

Most products for the treatment or prevention of human disease are studied in adequate and well-controlled clinical trials that enroll patients with the disease, and these clinical trials, along with other investigations and studies, serve as the basis for approving or licensing the product. However, inhalational anthrax is not a naturally occurring disease (occupational exposure has been eliminated) and human studies cannot be conducted because it would not be ethical or feasible to conduct studies in humans (intentional exposure is not ethical). In situations such as this, where human efficacy studies cannot be conducted because it would be unethical to deliberately expose healthy human volunteers to a lethal or permanently disabling toxic biological, chemical, radiological, or nuclear

[15] Request For Comments: 62 FR 40996 (July 31, 1997); Proposed Rule: 64 FR 53960 (Oct 5, 1999); Final Rule: 67 FR 37988 (May 31, 2002); Regulations: 21 CFR § 314.600-650 (New Drugs), § 601.90-95 (Biologics)

substance, and field trials to study the product's efficacy after an accidental or hostile exposure to the agent have not been feasible, efficacy of new products (e.g., raxibacumab for the treatment of inhalational anthrax) need to be derived from animal model of infection studies.

To address this situation, and provide a regulatory mechanism to accept efficacy from such animal models, FDA published a Final Rule in 2002 titled "New Drug and Biological Drug Products; Evidence Needed to Demonstrate Effectiveness of New Drugs When Human Efficacy Studies Are Not Ethical or Feasible,"[16] that is also referred to as the "Animal Rule." As noted above, this rule applies when adequate and well-controlled studies in humans cannot be ethically conducted and field efficacy studies are not feasible. In such circumstances, products intended to reduce or present serious or life-threatening conditions may be approved for marketing based on evidence of effectiveness derived from appropriate studies in animals and additional supporting data.

This rule is summarized in the Code of Federal Regulations (CFR), in Title 21 CFR 314.600 (Subpart I) for New Drugs and in Title 21 CFR 601.90 (Subpart H) for Biologic Products. Raxibacumab is a monoclonal antibody, and therefore, the provisions of 21 CFR 601.90 (Subpart H) regulations apply. Excerpts and summaries from the Final Rule and the CFR are provided below and describe the type of evidence and information that need to be provided to the FDA for determination of efficacy.

2.3.1 Criteria for Submission

Because inhalational anthrax is not a naturally occurring disease (occupational exposure has been eradicated, intentional exposure is not ethical), efficacy of new products for the treatment of inhalational anthrax need to be derived from animal model of infection studies. In January 2009, FDA published a draft *Guidance for Industry: Animal Models – Essential Elements to Address Efficacy Under the Animal Rule*,[17] which provides information on the development of animal models to study efficacy, including the critical characteristics of an animal model that need to be addressed under the Animal Rule. For example, these elements include the characteristics of the agent that causes the disease (in this case *B. anthracis*), the host susceptibility and response to the agent, the natural history of the disease in humans and comparability in animal models, the trigger and timing of intervention, the characteristics of the medical intervention, and study design considerations.

All animal studies subject to this rule must be conducted in accordance with preexisting requirements under good laboratory practices.

Safety evaluation of products is not addressed in the Animal Rule. Products evaluated for effectiveness under Subpart I of part 314 for drugs and Subpart H of part 601 for biological products (e.g., monoclonals) are expected to be evaluated for safety under preexisting requirements for establishing the safety of new drug and biological products. FDA believes that the safety of most of these products can be studied in human volunteers similar to those who could potentially be exposed to the product. Information on the safety of the product, immunogenicity, as well as potential drug

[16] Final Rule published in the Federal Register, Vol. 67, No. 105, May 31, 2002, pages 37988-37998; Regulations: 21 CFR § 314.600-650 (New Drugs), 21 CFR § 601.90-95 (Biologics)

[17] http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm065014.htm

interactions (e.g., raxibacumab and antimicrobial) is expected. FDA recognizes that some safety data, such as data on possible adverse interactions between the toxic substance itself and the new product, may not be available.

2.3.2 Criteria for Approval

The Animal Rule states that a biologic (e.g, raxibacumab) can be approved on the basis of adequate and well-controlled animal studies when the results of those animal studies establish that the biological product is reasonably likely to produce clinical benefit in humans. In assessing the sufficiency of animal data, FDA may take into account other data, including human data, available to the Agency. FDA will rely on the evidence from studies in animals to provide substantial evidence of the effectiveness of these products only when:

- There is a reasonably well-understood pathophysiological mechanism of the toxicity of the substance and its prevention or substantial reduction by the product;
- The effect is demonstrated in more than one animal species expected to react with a response predictive for humans, unless the effect is demonstrated in a single animal species that represents a sufficiently well-characterized animal model for predicting the response in humans;
- The animal study endpoint is clearly related to the desired benefit in humans, generally the enhancement of survival or prevention of major morbidity; and
- The data or information on the kinetics and pharmacodynamics of the product or other relevant data or information, in animals and humans, allows selection of an effective dose in humans.

Therefore, data from appropriate studies to address each of the above bullet points would need to be provided to support the conclusion that the product is effective.

In addition, approval under this regulation will be subject to three requirements:

1. Postmarketing studies. The applicant must conduct postmarketing studies, such as field studies, to verify and describe the biological product's clinical benefit and to assess its safety when used as indicated when such studies are feasible and ethical. A commitment to conduct such studies is typically included in the letter to the applicant that their biological licensing application (BLA) is "approved." Such postmarketing studies would not be feasible until an exigency arises. When such studies are feasible, the applicant must conduct such studies with due diligence. Applicants must include, as part of their application, a plan or approach to postmarketing study commitments in the event such studies become ethical and feasible.
2. Approval with restrictions to ensure safe use. If FDA concludes that a biological product shown to be effective under this regulation can be safely used only if distribution or use is restricted, FDA will require such postmarketing restrictions as are needed to ensure safe use of the biological product, commensurate with the specific safety concerns presented by the biological product, such as:
    - Distribution restricted to certain facilities or health care practitioners with special training or experience;
    - Distribution conditioned on the performance of specified medical procedures, including medical followup; and
    - Distribution conditioned on specified recordkeeping requirements.

3. Information to be provided to patient recipients. For biological products or specific indications approved under this subpart, applicants must prepare, as part of their proposed labeling, labeling to be provided to patient recipients. The patient labeling must explain that, for ethical or feasibility reasons, the biological product's approval was based on efficacy studies conducted in animals alone and must give the biological product's indication(s), directions for use (dosage and administration), contraindications, a description of any reasonably foreseeable risks, adverse reactions, anticipated benefits, drug interactions, and any other relevant information required by FDA at the time of approval. The patient labeling must be available with the product to be provided to patients prior to administration or dispensing of the biological product for the use approved under this subpart, if possible.

FDA may withdraw approval if:

- A postmarketing clinical study fails to verify clinical benefit;
- The applicant fails to perform the postmarketing study with due diligence;
- Use after marketing demonstrates that postmarketing restrictions are inadequate to ensure safe use of the drug product;
- The applicant fails to adhere to the postmarketing restrictions applied at the time of approval under this subpart;
- The promotional materials are false or misleading; or
- Other evidence demonstrates that the drug product is not shown to be safe or effective under its conditions of use.

3. Microbiology of Anthrax

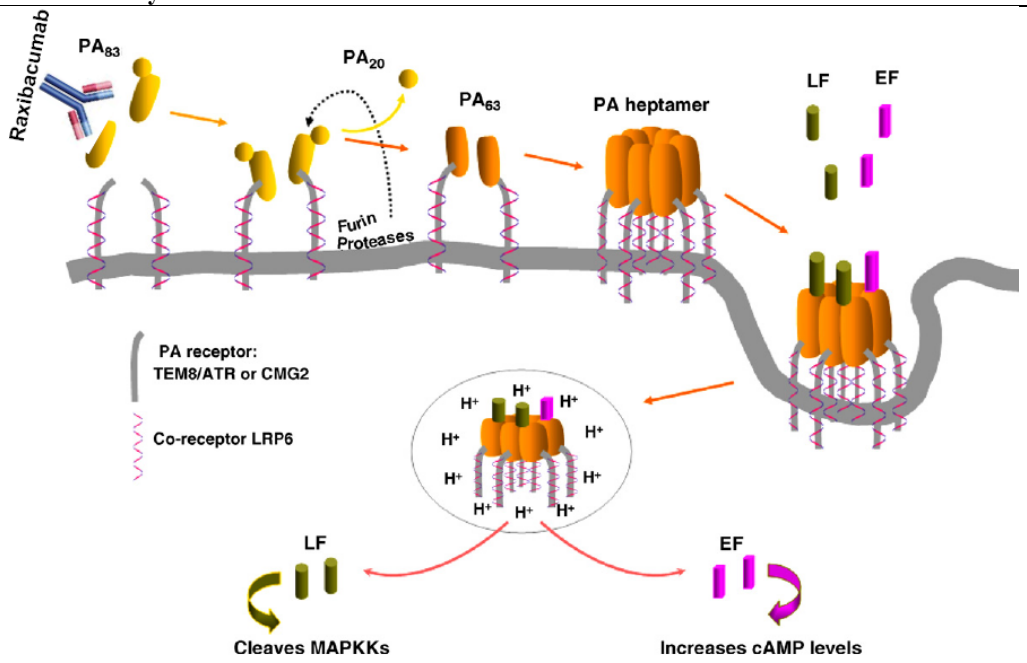
3.1 Proof of Concept Studies

HGS conducted a number of proof-of-concept studies to characterize the activity of raxibacumab against several strains of *B. anthracis* (*in vitro*), to evaluate the effect of raxibacumab in a rat toxin model (*in vivo*), and to evaluate the effect of raxibacumab in rabbit and monkey models of post-exposure prophylaxis when administration of raxibacumab occurred before or shortly after aerosol exposure to anthrax spores. A summary of these studies is provided.

3.1.1 Mechanism of Action

In vitro studies demonstrated that raxibacumab binds PA in supernatants from Sterne, Ames and Vollum strains of *B. anthracis*. The mechanism of action appears to be by neutralization of free PA. Studies show that PA binds the surface of human and murine macrophages, and the epitope on recombinant PA that binds the cell surface receptor appears to be the same as the one binding raxibacumab (Figure 2)[5], thereby suggesting that some structural similarity between the antigen recognition site on raxibacumab and the cell surface receptors binding site for PA exists. Raxibacumab blocks cAMP induction by recombinant ET when PA is preincubated with raxibacumab prior to addition of EF. Similarly, raxibacumab inhibits killing of murine macrophage (J774-A.1) cells when PA is preincubated with raxibacumab prior to addition of LF.

Figure 3.1.1-1. Entry of Anthrax Toxin into Cells and the Site of Action of Raxibacumab[5]



PA_{83} binds one of two cellular receptors, TEM8/ATR or CMG2, which have been reported to be associated with the LRP6 co-receptor. After binding, PA_{83} is cleaved by cellular proteases, such as furin, and the small PA_{20} fragment is released. PA_{63} then forms a ring-shaped heptameric pre-pore, which can simultaneously bind up to three molecules of LF and/or EF. The toxin/receptor complex is then internalized.. The endocytic vesicles are subsequently acidified, initiating a conformational change of the PA heptamer which converts it from the pre-pore into a mature pore that allows entry of EF and/or LF into the cell cytoplasm. LF is a protease targeting specific MAPKKs. EF is an adenylate cyclase that increases cAMP formation in cells. Raxibacumab blocks the ability of PA to bind its cellular receptors.

3.1.2 Activity *in vivo*

Rat Toxin Model

The effect of raxibacumab was evaluated in a toxin rat model. In F344 rats, intravenous (IV) administration of raxibacumab at a concentration of ten-fold the concentration of recombinant PA (rPA), administered up to three weeks prior to challenge with rLT (rLF + rPA), resulted in 100% survival for 24 hours. Isotype antibody treated control rats died within 90 minutes of LT administration. In SD rats given a slow infusion with the LD_{50} dose of rLT, treatment with raxibacumab at 0, 3, 6, 9, and 12 hours after the beginning of the infusion also improved survival at 24 hours. However, the number of rats surviving in the placebo group (35/48; 73%) was much higher than the expected 50% survival rate, so the results should be interpreted with caution. Survival beyond 24 hours was not measured.

Rabbit Models of Pre-exposure and Post-exposure Prophylaxis.

The effect of raxibacumab in pre-exposure and post-exposure prophylaxis was evaluated in New Zealand White rabbits. These studies were conducted as good laboratory practices (GLP) studies.

The applicant evaluated the effect of a single IV dose of 40 mg/kg raxibacumab administered at 0, 12, 24, or 36 hours post-exposure on survival in rabbits. The LD_{50} dose determined by Zaucha *et al*.

(1998)[18] was the basis for the aerosol exposures with 100 LD_{50} of *B. anthracis* Ames strain spores. The LD_{50} dose varied from 13-244 LD_{50}. There was no relationship between animals that received low LD_{50} doses of *B. anthracis* and survival. Raxibacumab, at a single dose of 40 mg/kg, was more effective in improving survival when administered at the time of infection or 12 hours post exposure (Table 1). All rabbits were abacteremic on day 28 post exposure. However, if the treatment was initiated at 24 or 36 hours post exposure, the survival decreased to 50% and 42%, respectively. Bacteremia was not measured after initiation of treatment.

In another experiment, the efficacy of single doses (5, 10, 20, or 40 mg/kg) of raxibacumab administered IV at 24 or 36 hours post-exposure was measured. Bacterial cultures and necropsies were not done. A single IV dose of 20 mg/kg raxibacumab administered at 24 hours post exposure was more effective in improving survival up to 14 days, when compared to the placebo treated rabbits (p= 0.0373; Table 3.1.2-1). Survival in the other treatment groups, including the highest dose tested (40 mg/kg), was not different from the placebo group. The median time to death in the rabbits treated with 20 mg/kg raxibacumab was six days while the median time to death in the other raxibacumab treatment groups ranged from 2.5 to 3.5 days. The reasons for a lower survival rate in the rabbits that received 40 mg/kg of the monoclonal antibody are unknown, but may be related to the inherent variability in this experimental model. Initiation of treatment at 36 hours post infection was not effective in improving survival.

Table 3.1.2-1. Summary of Survival Data in NZW Rabbits Treated with Raxibacumab at Various Times After Aerosol Exposure to Spores from the Ames Strain of *B. anthracis*

Treatment Group (Raxibacumab dose)	Time of Treatment (hours PI)	Survivors at 14 Days PI*	Median Time to Death Days PI (range)	Bacteremic at Time of Treatment
Experiment 1:				
1 (Placebo)	0	1/12 (8 %)	(2 – 3)	0/12 (0 %)
2 (40 mg/kg)	0	12/12 (100 %)	NA	0/12 (0 %)
3 (40 mg/kg)	12	12/12 (100 %)	NA	0/12 (0 %)
4 (40 mg/kg)	24	6/12 (50 %)	(1 – 3)	1/12 (8 %)
5 (40 mg/kg)	36	5/12 (42 %)	(2 – 4)	9/12 (75 %)
Experiment 2:				
1 (Placebo)	0	0/12 (0 %)	3 (1-4)	Not measured
2 (5 mg/kg)	24	3/12 (25 %)	3.5 (1-4)	Not measured
3 (10 mg/kg)	24	4/12 (33 %)	2.5 (1- 3)	Not measured
4 (20 mg/kg)	24	5/12 (42 %) *	6.0 (2 - 8)[#]	Not measured
5 (40 mg/kg)	24	4/12 (33 %)	2.5 (2 -8)	Not measured
6 (20 mg/kg)	36	0/12 (0 %)	3.0 (1- 9)	Not measured

Note: No rabbits died during the additional 28 day observation period in experiment 1
*Statistically different from placebo; p = 0.0373
[#]Statistically different from placebo; p = 0.0020

In another experiment, raxibacumab was administered at different doses (1, 5, 10, or 20 mg/kg) subcutaneously (SC) two days prior to exposure (aerosol challenge) or intravenously (40 mg/kg) within one hour of challenge with *B. anthracis* spores. No histopathology was done. Raxibacumab doses of 5, 10, and 20 mg/kg administered subcutaneously (SC) two days prior to spore challenge increased survival and reduced bacteremia. All rabbits receiving 40 mg/kg raxibacumab by the IV route within one hour of infection survived until 14 days post exposure. Gross necropsies were done

[18] Zaucha, GM et al. The pathology of experimental anthrax in rabbits exposed by inhalation and subcutaneous inoculation. 1998. Arch, Pathol. Lab. Med. 122(11): 982-92.

on all animals, and gross lesion incidences were largely dose-dependent, with greatly reduced numbers of lesions in the SC 10 and 20 mg/kg raxibacumab treatment groups and virtually no gross lesions present in the rabbits receiving IV 40 mg/kg raxibacumab. Also, hemorrhages in the brain/meninges occurred only in the 1 (5/12), 5 (2/7), and 10 (1/2) mg/kg raxibacumab SC treated groups. The reason(s) for this are unclear, but such lesions are rare in rabbits with untreated anthrax.[18]

Cynomolgus Monkeys: Pre-exposure prophylaxis.

The effect of raxibacumab was also evaluated in pre-exposure prophylaxis in Cynomolgus monkeys in a GLP study. The efficacy of 10, 20, or 40 mg/kg raxibacumab was evaluated in juvenile macaques by SC administration of raxibacumab two days prior to exposure (aerosol challenge) with spores from the Ames strain of *B. anthracis*. Survivors were followed for an additional 11 months and were re-challenged with spores from the Ames strain of *B. anthracis*. Raxibacumab improved dose dependent survival at all dose levels evaluated with 90% survival at the highest dose (40 mg/kg) tested (Table 3.1.2-2).

Table 3.1.2-2. Survival Results in Cynomolgus Monkeys at Day 28 PI following SC Prophylactic Treatment of Inhalational Anthrax with Raxibacumab*

Treatment	Dose (mg/kg)	LD_{50} Dose (mean ± SD)	Survivors / Total Infected	Time to Death for Animals That Died (Days)
Placebo	0	180 ± 72	0/10	2-5
Raxibacumab	10	187 ± 52	6/10	4-6
Raxibacumab	20	177 ± 61	7/10	4-6
Raxibacumab	40	194 ± 79	9/10	3

All treatments administered by the SC route two days prior to aerosol challenge with *B. anthracis* spores.
*Survivors were observed for an additional 60 days. There were no additional deaths during this 60-day observation period.

All surviving monkeys had negative blood cultures at each time point evaluated, but it is unknown whether or not the survivors were bacteremic soon after challenge. The major gross lesions seen in monkeys that died or were euthanized are shown in Table 3.1.2-3. The most common anthrax related lesions were splenic enlargement, enlargement and/or discoloration (hemorrhage) of lymph nodes (especially bronchial), and edema and/or hemorrhages in various organs. A higher proportion of monkeys in the raxibacumab treatment groups had hemorrhages in the brain/meninges (8/8) than was seen in the control animals (4/10). The reason(s) for this is unclear.

Table 3.1.2-3. Gross Lesions in Cynomolgus Macaques that Died, Infected with *B. anthracis* Following SC Prophylactic Treatment with Raxibacumab					
Organ	**Diagnosis**	**Monoclonal Anti-PA Antibody Dose (mg/kg) (# Affected/ Total Died)**			
		0	**10**	**20**	**40**
External Exam	Bloody Nasal Discharge	2/10	0/4	0/3	0/1
Adrenal Glands	Hemorrhage(s)	3/10	0/4	0/3	1/1
Brain, Meninges	Hemorrhage(s)	4/10	4/4	3/3	1/1
Body Cavities (Any)	Fluid or Hemorrhage	3/10	0/4	2/3	0/1
Lungs	Discoloration or Hemorrhages(s)	3/10	0/4	0/3	1/1
Lymph Nodes (Any)	Discolored/Enlarged/ Hemorrhage(s)	6/10	1/4	0/3	0/1
Lymph Node- Bronchial	Discolored/Enlarged/ Hemorrhage(s)	5/10	1/4	0/3	0/1
Mediastinum	Discolored/Enlarged/ Hemorrhage(s)	1/10	0/4	0/3	0/1
Skin-Subcutis	Edema or Hemorrhage	3/10	0/4	0/3	0/1
Spleen	Enlarged	9/10	3/4	1/3	1/1

The surviving 22 monkeys were observed for a total of 11 months post exposure, and then 21 monkeys were re-challenged with 100 LD_{50} of Ames strain *B. anthracis* spores (one monkey died of non-anthrax related causes). A group of six, non-research-naïve, Cynomolgus monkeys (naïve to anthrax and to monoclonal anti-PA antibody) served as positive anthrax aerosol controls. All 21 of the surviving monkeys from the original prophylaxis study survived up to 28 days after re-challenge. All six positive control animals died by day six post exposure, were bacteremic at the time of death, and 5/6 had gross lesions that were consistent with anthrax.

Serum was collected for the cAMP ET neutralization assay and the anti-PA assay from all surviving monkeys at six and 11 months after the initial challenge as well as 14 and 28 days after re-challenge. All surviving monkeys had neutralizing antibody titers following the initial exposure to *B. anthracis* spores, and the titers increased following the second exposure to *B. anthracis*. Surviving monkeys mounted an antibody response after the first challenge with *B. anthracis* spores so prophylactic treatment with raxibacumab did not prevent induction of an immune response capable of responding to the second challenge with *B. anthracis* spores. The increase in neutralizing antibody titers, as measured by the fold change in titer, from six months post-exposure to after the second challenge, was significantly lower ($p = 0.04$) in the 10 mg/kg treatment group (fold change was 19 ± 11) than in the 20 and 40 mg/kg treatment groups (fold changes were 66 ± 29 and 70 ± 45, respectively). The reason for the lower fold change in the 10 mg/kg treatment group is unknown.

The pre-study serum samples from all monkeys had positive anti-PA titers before the first exposure to *B. anthracis* spore aerosols. The reason for this is unknown, but strongly suggests that the assay was not specific for anti-PA antibodies.

3.1.3 Microbiologic Measurements in Animal Efficacy Studies

Microbiologic measurements in the animal efficacy studies included culture, detection of PA by electro-chemiluminescent (ECL) assay, and polymerase chain reaction (PCR). Culture is considered to be an established method for detection of bacteremia and is recommended as a biomarker for therapeutic intervention. Detection of PA by ECL assay and DNA by PCR assay is considered experimental.

Culture of Blood and Tissues from Infected Animals.

Cultures were done by direct inoculation of samples of whole blood or homogenized tissues onto 5% sheep blood agar or trypticase soy agar, depending on the individual experiment. Although sheep blood agar should be a better medium for recovery from infected animals due to the highly enriched nature of the agar, either agar should promote growth of *B. anthracis.* All blood for cultures was collected with EDTA anticoagulant, which is known to decrease recovery of bacteria from blood.[19,20] Also, the volume of blood (10 to 40 μL) and homogenized tissues used to inoculate agar plates was small. In pediatric patients, 3 to 5 mL of blood is typically used for blood cultures. Use of such small volumes of blood from animals where there are only a few bacteria present, and collection of the sample in EDTA anticoagulant, led to false negative results. Also, the laboratory did not always follow the protocol regarding the volume of inocula used or incubation times for cultures.

Electrochemiluminescence Assay.

A screening and a quantitative ECL assay was designed for the purpose of detecting PA, as a biomarker, in **serum** from infected rabbits and monkeys to use as a trigger for intervention in efficacy studies. **Plasma** samples were used in the rabbit study that evaluated the efficacy of raxibacumab in combination with levofloxacin. The principle and methodology of the ECL assay were based on that of ELISA with rabbit polyclonal anti-PA antibodies tagged either to biotin or a Sulfo luminescent compound. The lower limit of detection (LOD) and lower limit of quantitation (LOQ) of the assays in rabbits and monkeys are summarized in Table 3.3.3-1. Overall, the results suggest that the ECL assay has a high level of sensitivity. However, shortcomings of the ECL tests in both rabbits and monkeys exist. Common to both are the inadequacies related to specificity and precision (for details, see Appendix-1). The testing of **cross-reactivity** was limited to edema factor at a concentration of 5.0 ng/mL. The testing of cross-reactivity against only EF of *B. anthracis* is inadequate. Other possible sources of cross-reactivity or nonspecific binding such as with bacterial species other than *B. anthracis* were not evaluated. The shortcoming of specificity testing is further highlighted in the screening ECL assay for PA in rabbit serum when 7/46 (15%) normal rabbit serum samples showed positive findings. In the rabbit quantitative PA assay, 4/30 (13 %) of normal rabbits also gave **false-positive results**. Although the false positive results were lower in monkeys, it is important to note that these results are based on high acceptance criteria ≤ 20 (≤ 25% at the lower limit of quantitation) and variability suggesting low precision.

[19]Murry, PR et. al.(eds). 2003. Manual of Clinical Microbiology. American Society for Microbiology Press, Washington, DC, USA.

[20]Clinical and Laboratory Standards Institute. 2007. Principles and procedures for blood cultures; Approved Standard M47-A. Clinical and Laboratory Standards Institute, Wayne, PA. USA.

Table 3.1.3-1. Cutoff limits and variability ranges for Rabbit and Monkey ECL assays for detection of PA				
Test	**LOD (ng/mL)**	**LOQ (ng/mL)**	**ULOQ (ng/mL)**	**% Coefficient of Variation***
Rabbits:				
Screening (Serum)**	0.4	NA	NA	9 - 24 %
Quantitative (Serum)	0.114	0.17	20.5	7 - 38 %
Screening (Plasma)	0.5	NA	NA	13 - 22 %
Quantitative (Plasma)	NA	0.14	125	6 – 15 %
Monkeys:				
Screening (Serum)	1	NA	NA	19 – 39 %
Quantitative (Serum)	0.065	0.065	144.5	10 – 19 %

LOD = Lower limit of detection; **LOQ** = Lower limit of quantitation;
ULOQ = Upper limit of quantitation.
*Total (%CV) for positive control samples and represents data from both HGS and Battelle laboratories and acceptable limits were set based on a publication by Findlay *et al*., 2000[Error! Bookmark not defined.].
**15% normal rabbit sera positive at Battele laboratory

Some of the serum samples from rabbits and monkeys were positive by the screening and quantitative ECL assay prior to enrollment in the efficacy studies (for details see Appendix – 1).

PCR.
The Real-time PCR assays were well planned and executed. The pagA assay identified the presence or absence of the pOX1 plasmid containing the target gene sequences from *B. anthracis*. The %CVs are very low indicating a high level of precision. The major shortcoming of this assay was the need to provide proof of specificity (for details, see Appendix 1).

Conclusions:
The measurement of PA by ECL assay, as standardized, is not reliable and showed high variability and lack of specificity. It is recommended that cure rates be based on presence of bacteremia at the time of initiation of treatment and not ECL assay or PCR positive findings.

4. Anthrax Disease – Natural History in Animal Models

4.1 Background

In order to be able to develop a novel therapeutic product such as raxibacumab for the treatment of inhalational anthrax, it was important to identify and characterize animal models of inhalational anthrax to be used to evaluate product's efficacy. Specifically, as provided in the Animal Rule, it was important to first study the natural history of the anthrax infection in the animal, with the goal to understand, reasonably well, the pathophysiological mechanism of the toxicity of the substance (*B. anthracis* toxin) and its prevention or substantial reduction of disease and/or mortality by the product (raxibacumab). After consideration of rodent and larger animal species, the natural history of anthrax in Cynomologus monkeys and New Zealand White rabbits was evaluated, and these animals were subsequently used for the evaluation of raxibacumab efficacy in randomized comparative studies.

4.2 Cynomolgus Monkey

The natural history of inhalational anthrax was studied in the Cynomolgus monkey to compare the similarities and differences to human disease.

Study design*:* This was a non-GLP study in eight healthy, adolescent to young adult Cynomolgus monkeys (*Macaca fascicularis*) infected with a target dose of 200 LD_{50} (range 167 to 451 x LD_{50}). Adult Cynomolgus monkeys that had survived monkey pox experiments were used for the model characterization study. The dose of *B. anthracis* Ames strain spores used was based on the LD_{50} determined previously by USAMRIID and Battelle Laboratories.[21] Temperature was monitored by telemetery every hour. Blood samples were collected every six hours until 72 hours post-infection (PI) and at days 4, 5, 6, 7, 8, 14, 21, and 30 days PI for culture, detection of PA, and *B. anthracis* PCR. Sera were collected for detection of PA by the quantitative ECL assay and the presence of neutralizing PA antibodies by toxin neutralization assay (TNA). Animals were followed for up to 30 days PI. Terminal samples were taken, when possible, from any animal found dead or just prior to euthanasia if the animal was moribund. Gross necropsies were performed on all monkeys that died or were euthanized but systematic, comprehensive, necropsies were not done. Survivors were not necropsied (for details, see Appendix 2).

Outcome

- Of the eight monkeys, two (25%) survived; the infection was documented by culture, PCR, serum PA concentrations, and development of anti-PA antibodies. The monkeys were not necropsied. The reasons for survival are unknown.

- All of the monkeys that died (n =6) had gross or microscopic lesions consistent with anthrax but systematic, comprehensive, necropsies were not done. Thus, pathology cannot be easily compared to published data[21] or the pivotal efficacy study.

- Serum PA concentration kinetics were triphasic (rise-plateau-rise), but terminal samples may be artificially high due to the delay in collecting samples at necropsy.

- In monkeys that survived, the peak serum PA concentrations occurred later and were lower than in the animals that died.

4.3 New Zealand White Rabbit

The natural history of inhalational anthrax was studied in the New Zealand White rabbits to compare the similarities and differences to human disease.

Study Design: This was a non-GLP study in eight young adult New Zealand White rabbits infected with a target aerosolized dose of 200 LD_{50} (range 93-278 LD_{50}) that was based on the LD_{50} dose in a previously conducted study by USAMRIID.[18] One rabbit did not die from inhalational anthrax during the study period. The animals were followed for clinical signs and symptoms of disease, and microbiologic and hematological parameters for up to 7 days post-infection (PI). From

[21] Vasconcelos, D *et al*. Pathology of inhalation anthrax in cynomolgus monkeys (*Macaca fascicularis*). 2003. Lab. Invest. 83(8): 1201-9.

approximately 18 to 48 hours PI, rabbits were observed hourly (± 10 minutes) for clinical signs of illness. After 48 hours, rabbits were observed for abnormal clinical signs twice daily until Day 7. Blood samples were collected every four hours until 36 hours PI and at 48, 60, and 72 hours PI for culture, detection of PA, and *B. anthracis* PCR. Cultures were performed, and *B. anthracis* identified, using the same methods as in the monkey model characterization experiment (for details, see Appendix 2).

Outcome

- Of the eight infected rabbits, four died by 3 days PI and seven died by 117 hours (i.e., 5 days post-infection with a mean time of death of 95.5 ± 37.5 hours. In the rabbit that survived, the blood cultures, quantitative PA/ECL assay, and PCR were positive when the rabbit was euthanized at 7 days PI.

- The mean time to death (most conservative estimate, 85.1 ± 25.4 hours) was >24 hours longer than that reported by Zaucha *et al*.[18] The reason for this is unclear.

- No necropsies were done so lesions could not be compared to published reports by Zaucha *et al*.[18]

- The time to first > 2°F temperature increase was highly variable (mean ± standard deviation = 31.1 ± 21.7 hours) suggesting that temperature increase was not a consistent indicator of early disease and may not be a good trigger for intervention.

- Cultures of blood were positive in 4/8 rabbits by 24 hours PI and in 7/8 rabbits by 36 hours PI. The median time to a positive culture was 26 hours.

- There was an increase in PA concentration corresponding to the advent of positive cultures for *B. anthracis* and concentrations of PA increased with time PI. In general, the PA concentrations were tri-phasic (rise-plateau-rise), but these results should be interpreted with caution because of variability in the quantitative assay and delay in collecting samples at necropsy.

4.4 Interspecies Comparison

Table 4.4-1 represents the summary of nonclinical and clinical data from the published literature as well as the sponsor collected nonclinical data from natural history and pivotal/combination animal studies, and compares the similarities and differences of anthrax infection, host susceptibility and response, pathophysiology, triggers for intervention, and measure of outcome between human disease and the monkey and rabbit models of disease.

Table 4.4-1 Interspecies Comparison

DATA ELEMENTS	Animal		Human
	Rabbit	NHP	
A. Characteristics of the CBRN Agent that Influence the Disease or Condition			
1. The challenge agent	Ames strain *B. anthracis* spores	Ames strain *B. anthracis* spores	Many strains, but Ames strain used in 2001 bioterrorism attack
2. Pathogenic determinants	Pathogenesis, mechanism of toxicity similar to humans	Pathogenesis, mechanism of toxicity similar to humans	
3. Route of exposure	Aerosol challenge with 200x the LD50 of *B. anthracis*	Aerosol challenge with 200x the LD50 of *B. anthracis*	Inhalation, ingestion or cutaneous
4. Quantification of exposure	Specific number of spores administered to each animal which was above the threshold at which human disease would occur	Specific number of spores administered to each animal which was above the threshold at which human disease would occur	N/A
B. Host Susceptibility and Response to Etiologic Agent	Susceptible to *B. anthracis* infection when exposed to aerosolized spores by inhalation[1]. Pathology of anthrax in rabbit model similar to inhalational anthrax in humans[2]	Rhesus, African Green, and Cynomolgus Monkeys susceptible to *B. anthracis* infection when exposed to aerosolized spores by inhalation. For the most part, all three species demonstrate lesions that are similar to each other and to human but there are subtle differences.[3-6]	Susceptible
C. Natural History of Disease: Pathophysiologic Comparability			
1. Time to onset of disease/condition	More rapid than humans[2]	Similar to that seen in humans but dependent on the dose used for the challenge.[4,5] At the LD_{50} dose for cynomolgus macaques (6.2×10^4 CFU), death probably more rapid than humans	Prodromal phase 1-6 days; fulminant phase less than 24 hours[7]
2. Time course of progression of disease/condition	More rapid than humans	Similar to that seen in humans but dependent on the dose used for the challenge.[4,5] At $\geq 2 \times 10^5$ CFU, death within 4 days.	Overall mortality of 85% with a mean time from symptom onset to death of 4.8 days[7] In 2001 attacks, symptoms began

			4-6 days.[8] In Sverdlovsk incident, death in 1-4 days.[9]
3. Manifestations (signs and symptoms)	Lethargy, not eating, rapid respirations/respiratory distress, seizure and/or moribund	Few clinical signs until 1-2 hours prior to death, then progressively less responsive to external stimuli. Lethargy, tachycardia, and fever, although abnormal signs were individualized and did not present long before death.[6]	Flu-like symptoms for several days followed by severe respiratory collapse
D. Trigger for Intervention	Positive PA level or temperature elevation	Positive PA level	Circumstance specific – medical history, epidemiologic history, signs and symptoms
E. Characterization of the Medical Intervention			
1. Product class	Raxibacumab - first in class		
2. Mechanism of action	Human monoclonal antibody which binds the protective antigen (PA) of *B. anthracis* and prevents the binding of PA with its receptors		
4. Activity in disease/condition of similar pathophysiology	N/A		
5. PK in unaffected animals/humans	Studies in healthy human subjects		
6. PK/PD in affected animals/humans	Humans achieve similar to or greater exposure to raxibacumab following a single 40 mg/kg IV dose compared to rabbits and monkeys receiving the same dose. Mean raxibacumab Cmax in humans following a single 40 mg/kg IV dose was similar to or greater than mean Cmax values in monkeys and rabbits. Mean raxibacumab AUCinf in humans following a single 40 mg/kg IV dose was 2.4 and 4.6-fold that of the mean Cmax values in monkeys and rabbits, respectively. Half-life of raxibacumab was longer in humans compared to mean half-lives observed in monkeys and rabbits (20.6 ± 6.5 days versus 10.1 ± 2.4 days and 4.1 ± 0.85 days, respectively).		
7. PK interactions with medical products likely to be used concomitantly	No interaction with levofloxacin	No interaction with ciprofloxacin	Exposure to ciprofloxacin has no consistent or meaningful impact on raxibacumab PK; ciprofloxacin exposure is equivalent when ciprofloxacin is administered alone and with raxibacumab

8. Synergy or antagonism of medical products likely to be used in combination	No interaction with levofloxacin	No interaction with ciprofloxacin	
F. Design Considerations for Animal Efficacy Studies	GLP, randomized, double-blind, placebo controlled study with mortality endpoints		
1. Endpoints	14 day survival, survival time	28 day survival, survival time	
2. Timing of intervention	Based on detection of positive PA level, or 2 consecutive temperature elevations, confirmed by culture	Based on detection of positive PA level, confirmed by culture	
3. Route of administration	IV	IV	IV
4. Dosing regimen	Single dose raxibacumab 40 mg/kg IV	Single dose raxibacumab 40 mg/kg IV	Single dose raxibacumab 40 mg/kg IV
HUMAN SAFETY INFORMATION			323 human subjects exposed to single and double dose raxibacumab

1. Phipps AJ, Premanandan C, Barnewall, RE, Lairmore, MD. Rabbit and nonhuman primate models of toxin-targeting human anthrax vaccines. Microbiol Mol Biol Rev. 2004 Dec;68(4):617-29.
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5. Efficacy Studies in Animal Models

Based on the results of the natural history studies of anthrax in NZW rabbits and Cynomolgus monkeys, these species were selected for the efficacy studies of raxibacumab as treatment of inhalational anthrax. Four treatment studies with raxibacumab were conducted. The initial two efficacy studies tested raxibacumab versus placebo; one study was conducted in rabbits and the other one in monkeys. Both of these studies demonstrated that the 40 mg/kg IV raxibacumab dose was superior to placebo.

The subsequent two studies evaluated the efficacy of raxibacumab plus antimicrobial (a fluoroquinolone) versus antimicrobial alone in the treatment of anthrax; a placebo arm was included in these studies as well. As designed the main purpose of these studies was to see whether there may be any antagonism when the two components are used together. However, it was also of interest whether raxibacumab made a contribution to the efficacy of the combination (raxibacumab and antimicrobial) and whether the efficacy of the combination was higher than the efficacy of antimicrobial alone. In these studies, unexpectedly, the efficacy of the antimicrobial (levofloxacin in rabbit and ciprofloxacin in monkey) was 95-100%, and similarly, high rates of efficacy were also seen in the raxibacumab plus antimicrobial combination arm. Given the high efficacy of the antimicrobial in these studies, it was not possible to demonstrate a contribution of raxibacumab to the efficacy of the regimen, raising the question about the need for an animal model that more closely approximates the 55% survival seen in 2001 in the patients with inhalational anthrax.

Analyses populations:
The analysis populations for the four efficacy studies were defined as follows:

Intention-to-treat (ITT): all animals that were randomized and challenged with *B. anthracis*. The ITT analysis was to be based on the treatment group planned at randomization rather than the actual treatment the animals received. Animals that were spore-challenged, but died before receiving placebo or active treatment, were to be included in this population as treatment failures.

FDA Primary: all animals that were bacteremic (defined as a positive blood culture) at the time of therapeutic intervention, and according to the actual treatment administered. FDA used this as its primary analysis population because both PA assays quantitative ELISA and ECL trigger for intervention exhibited high intra and inter animal variability as well as a significant operator-dependency. The FDA primary analysis using only animals that were bacteremic at the time of treatment was specified in order to clearly differentiate those animals that received raxibacumab for treatment as opposed to post-exposure prophylaxis.

As treated: all treated animals according to the actual treatment administered.

Toxemic at treatment: the ITT population according to the detection of toxemia at treatment, defined as the detection of PA by quantitative ECL.

Excluding non-anthrax death: the above analysis populations, excluding animal(s) that died from non-anthrax causes.

5.1 Raxibacumab versus Placebo

The efficacy of raxibacumab monotherapy was compared to placebo in the treatment of inhalational anthrax in two pivotal animal studies (Cynomolgus macaque and New Zealand White rabbit).

5.1.1 Cynomolgus Monkey

Study 724-G005829: "Evaluation of Raxibacumab Efficacy as Therapeutic Treatment Against Inhalation Anthrax in the Cynomolgus Macaque"

Objectives

- To evaluate the efficacy of raxibacumab when administered as a therapeutic treatment against lethality upon appearance of clinical symptoms due to inhalation exposure to *B. anthracis* in Cynomolgus monkeys.
- Although not pre-specified as primary or secondary study objectives in the protocol, additional objectives of this study were to determine the pharmacokinetics (PK) of raxibacumab following a single IV raxibacumab dose and the kinetics of *B. anthracis* PA in monkeys with inhalation anthrax.

Study Design

This was a randomized, double-blind, placebo-controlled efficacy study designed to evaluate single IV doses of raxibacumab vs. placebo as therapeutic treatment against lethality in cynomolgus monkeys with symptomatic inhalation anthrax. This study also evaluated the kinetics of *B. anthracis* PA and the PK of IV raxibacumab in symptomatic monkeys.

Methods

Forty naïve cynomolgus monkeys were randomized into two separate groups of 14 monkeys and one group of 12 monkeys (each group 50% male, 50% female) for treatment as delineated in the table 5.1.1-1 below:

Table 5.1.1-1 Treatment Groups

Group	Number of NHPs	Dose	Route/Frequency	Treatment Point
Group 1	14	40 mg/kg raxibacumab (1 mL/kg)	IV/single dose	Individual treatment times were based on serum PA levels as detected by ECL
Group 2	14	20 mg/kg raxibacumab (1 mL/kg)	IV/single dose	
Group 3 (placebo)	12	Raxibacumab buffer (1 mL/kg)	IV/single dose	

(Adapted from HGS' BLA submission, p.21)

The study was conducted at Battelle Biomedical Research Center (BBRC), West Jefferson, OH. Monkeys were randomized to 1 of 3 aerosol challenge days and a challenge order per day. On Study Day 0, monkeys were challenged with a targeted 200 x lethal dose (LD50) (1.24 x 107 spores) dose of *B. anthracis* spores (Ames strain) by a Collison nebulizer and delivered using a head-only inhalation exposure chamber.

After the animals completed aerosolization, they were observed twice daily throughout the study, with observations performed more frequently (every six hours) from approximately 24 through 192 hours post challenge. Body temperature was monitored hourly throughout the course of the study. Beginning at 24 hours through up to 54 hours post spore challenge, blood samples for culture and PA were taken every six hours up to the time of treatment.

When an animal exhibited a positive serum PA level via the ECL screening assay or at 54 hours post challenge, a single bolus IV injection of either 40 or 20 mg/kg raxibacumab, or 1 mL/kg raxibacumab buffer (dependent upon that animal's treatment assignment) was administered. Just prior to treatment intervention (± 5 minutes), monkeys were administered a single 1 mg/kg dose of diphenhydramine (or equivalent) intramuscularly (IM). Diphenhydramine was given to parallel the treatment paradigm for humans in Phase 2/3 studies. Staff members administering the study agent were blinded to study agent preparation to preclude introduction of bias into the study following treatment.

Death or euthanasia was recorded at the time observed and a complete necropsy was performed. Blood samples were collected during the study for hematology and CRP, as well as to measure bacteremia by culture and PCR, serum PA levels, anti-PA and TNA levels, and serum raxibacumab levels. Blood was collected 3 days prior to spore challenge, just prior to spore challenge, and 5 minutes, 12 and 24 hours, and 3, 5, 8, 14, and 28 days following treatment intervention. A terminal blood sample was also collected if possible.

Demographics and Anthrax Exposure

The treatment groups were comparable with respect to sex, weight, and age at randomization. The anthrax spore challenge by treatment group is shown in the table 5.1.1-2 below:

Table 5.1.1-2 Spore Challenge Exposure

	Placebo N=12	Raxibacumab 20 mg/kg N=14	Raxibacumab 40 mg/kg N=14	All Groups N=40	P-value[1]
Anthrax exposure (x LD_{50})					0.0255
N	12	14	14	40	
Mean ± SD	197.6 ± 43.5	199.0 ± 52.4	157.2 ± 32.4	184.0 ± 46.8	
Median	207.9	208.5	161.6	175.0	
Range	121.0-277.0	130.0-301.0	106.9-218.0	106.9-301.0	

[1] P-value based on 1-way ANOVA for comparison among all treatment groups
(Adapted from HGS' BLA submission, p.45)

The spore challenge dose was lower on average in the 40 mg/kg raxibacumab group than in the other two treatment groups. There were statistically significant differences in mean spore exposure levels among the three treatment groups (F test, p=0.0255). The p-values (t-test) for further pair-wise comparisons were 0.9413 for the 20 mg/kg raxibacumab group vs. placebo, 0.0123 for the 40 mg/kg raxibacumab group vs. placebo, and 0.0176 for the 20 mg/kg raxibacumab vs. 40 mg/kg raxibacumab groups. The difference in inhaled spores between the 40 mg/kg raxibacumab group and the placebo group was statistically significant even after the conservative Bonferroni multiplicity adjustment. Further examination of the three animals that

received the lowest challenge dose revealed that C23640 received the lowest dose at 106.9 x LD_{50} and died, C24823 received 112 x LD_{50} and survived, and C23655 received 116 x LD_{50} and died. There did not appear to be a relationship between challenge day, challenge dose, and survival.

The time to treatment for animals that were bacteremic at the time of treatment was 38.4±7.6 hours for the placebo animals (N=10), 43.2±8.3 hours for the raxibacumab 20mg/kg treated animals (N=12), and 43.1±4.3 hours for the raxibacumab 40 mg/kg treated animals (N=13). There were no statistically significant differences between the groups.

Statistical Methods

According to the HGS protocol, the primary efficacy analysis was to be subject to multiple comparison adjustment using a step-down sequential testing procedure.

The primary efficacy analysis was performed using a 2-sided likelihood test and was to be subject to multiple comparison adjustment using a step-down sequential testing procedure. First the 40 mg/kg raxibacumab group was compared with placebo. If this was statistically significant then the 20 mg/kg raxibacumab group was compared with placebo for statistical significance. Sensitivity analyses were to be performed for the as-treated population, HGS' modified ITT population, the FDA primary population, and the group of all animals that were randomized including any that were randomized but not challenged with spores.

Efficacy Results

Primary Endpoint

The primary efficacy endpoint was survival at Day 28. The efficacy described in Table 5.1.1-3 is based on the HGS ITT statistical analysis and the FDA primary statistical analysis of those animals that were bacteremic (as defined by positive blood culture) at the time of treatment.

Table 5.1.1-3 Primary Efficacy Results in Cynomolgus Monkeys (Day 28)

Population	Treatment	N	No. of Survivors (%)	P-value*	95% CI of Raxi-placebo**	97.5% CI of Raxi-placebo**
HGS ITT	Placebo	12	0 (0.0%)			
	20 mg/kg raxibacumab	14	7 (50.0)	0.0064	(19.3, 73.7)	(13.2, 77.0)
	40 mg/kg raxibacumab	14	9 (64.3)	0.0007	(31.6, 84.7)	(27.0, 87.4)
FDA Primary	Placebo	10	0 (0.0%)			
	20 mg/kg raxibacumab	12	5 (41.7%)	0.0396	(7.2, 68.7)	(1.5, 72.4)
	40 mg/kg raxibacumab	13	9 (69.2%)	0.0016	(31.1, 88.9)	(25.7, 90.9)

* P-values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.

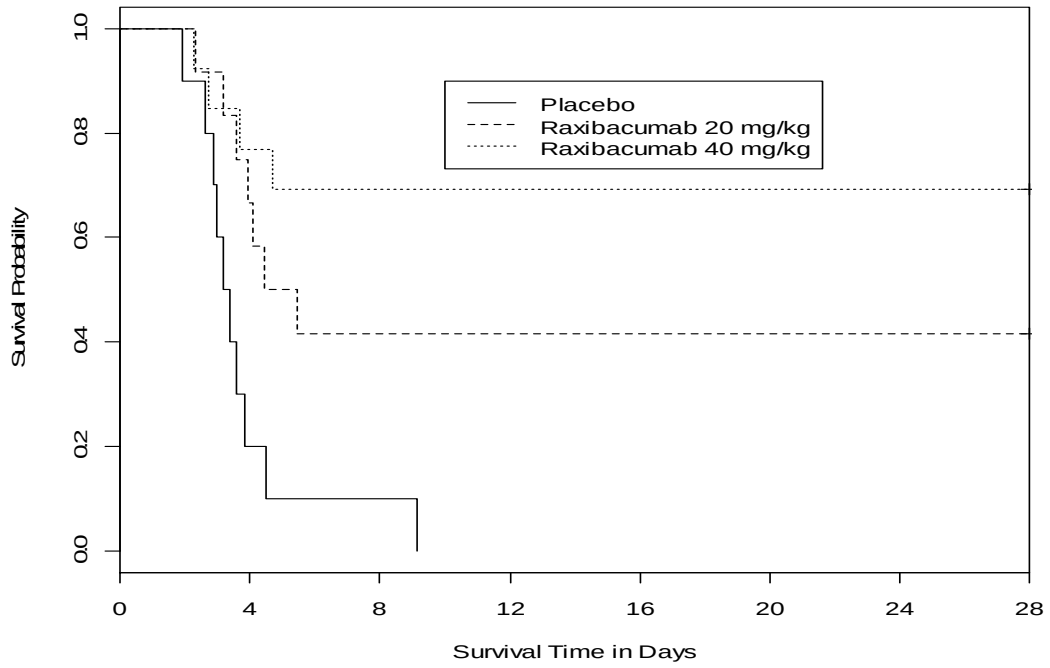
** CIs are exact confidence intervals.

HGS concluded that both the 20 mg/kg and the 40 mg/kg doses achieved a statistically significant mortality difference compared to placebo. For the FDA primary analysis, two animals in the placebo group, two animals in the raxibacumab 20 mg/kg group, and one animal in the raxibacumab 40 mg/kg group were excluded because they were not bacteremic at the time of treatment. After exclusion of these animals, both the 20 mg/kg and the 40 mg/kg doses achieved a statistically significant mortality difference compared to placebo for the FDA primary analysis.

Secondary Endpoint

The secondary efficacy endpoint was survival time, defined as the time from spore challenge to death during the 28 day study period. The figure below (Figure 5.1.1-1) is a graph of the Kaplan-Meier survival curves for the three treatment groups of the monkeys in the FDA primary analysis group. The median survival times were 3.3 days in the placebo group, 5.0 days in the raxibacumab 20 mg/kg group and beyond 28 days in the raxibacumab 40 mg/kg group because 69.2% of the animals survived at the end of the study. There was a statistically significant difference in terms of survival time among the three groups (log rank test, p=0.0006). Pairwise comparisons also show statistically significant differences between each raxibacumab group and the placebo ($p = 0.0098 < 0.025$ for 20 mg/kg group versus placebo, and $p = 0.0005 < 0.025$ for 40 mg/kg group versus placebo) after the Bonferroni adjustment for multiple comparisons (0.025=0.05/2).

Figure 5.1.1-1 Survival Probability of Monkeys in FDA Primary Analysis Population



PK analyses of raxibacumab concentration-time profiles for all raxibacumab-dosed monkeys were conducted using population analysis techniques with NONMEM software. Serum raxibacumab concentration-time data, serum PA concentration-time data, individual

raxibacumab PK parameters, individual PA kinetic parameters, serum anti-PA antibody concentrations, and serum TNA titers were summarized using descriptive statistics (see also **Section 6. Clinical Pharmacology** of this document.)

Other Parameters Measured

The majority of animals exhibited clinical signs consistent with anthrax following the spore challenge. The most common clinical features were lethargy, not eating, and respiratory abnormalities. Body temperature was monitored in all animals. An elevation in body temperature or loss of diurnal rhythm was noted at 2 to 4 days post-challenge and appeared to coincide with decreased activity in the majority of animals.

Laboratory Safety Results

CBC and Differential

WBC levels were stable in all monkeys through 24 hours post spore challenge, spiked and then declined to baseline levels between 24 to 48 hours post-challenge for most monkeys. For non-survivors, this decline was followed by WBC increases until the time of death. For the majority of survivors, WBC levels approached baseline levels for the remainder of the study. Platelet counts showed a decline after approximately 24 hours post challenge. In non-survivors, platelet counts continued to decline until the time of death. In survivors, the platelet count decline ended approximately at 72 hours and was followed by an upward trend through the end of the study. RBC levels began to decline in all animals through 24 hours post-challenge. In non-survivors, the decline continued until death. In survivors, the RBC levels started to trend in a positive direction approximately 168 hours post-challenge. Serial WBC differentials were recorded for all animals. The neutrophil percent increased following challenge but then subsided in surviving animals. Animals demonstrated decreasing levels of lymphocytes following a rapid spike post-challenge. Monocytes and eosinophils were slightly decreased with a trough at 24 hours post treatment. There was an increase in the basophil percentages in raxibacumab treated animals on day 5 post treatment. These hematologic data are most suggestive of a non-specific process associated with acute anthrax infection in these animals.

Necropsy and Histopathology

Necropsies were performed on all animals that died. The gross findings are outlined in the Table 5.1.1-4 below.

Table 5.1.1-4 Gross Pathology Findings in Cynomolgus Monkeys

Group	Placebo		Raxibacumab 20 mg/kg		Raxibacumab 40 mg/kg	
Number in Group	**12**		**14**		**14**	
Mortality	**100%**		**50%**		**36%**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**
Organ/Lesion #Dead	**6**	**6**	**4**	**3**	**2**	**3**
No Gross Lesions		1				1
Adrenal Gland, Discoloration					1	
Brain, Discoloration/foci/accumulation (red/dark)	1	2	3	3	1	2
Abdominal Cavity, Fluid	1	1				
Pericardial Cavity, Fluid		1	1			1
Thoracic Cavity, Fluid	1	1				
Bronchial Lymph Node, Enlarged	5	2	2	1	1	1
Mediastinal Lymph Node, Enlarged	4	1	2			1
Mesenteric Lymph Node, Enlarged	3				1	
Skeletal Muscle, Cyst			1			

(Adapted from HGS' BLA submission, p.533)

An increased number of the raxibacumab treated animals compared with placebo treated animals had evidence of discoloration/foci/accumulation on gross pathology. Based on this information, HGS was asked to perform histopathologic analysis on all tissues (with particular emphasis on the brains) for all animals that died during the study.

In Study 901-G005829 entitled, "Assessing the Terminal Pathology of Cynomolgus Macaques Aerosol Challenged with *Bacillus anthracis* and Treated with Raxibacumab or Placebo," Battelle examined the histopathology of the tissues collected in study 724-G005829. Table 5.1.1-5 summarizes the findings in the brain.

In summary, more numerous and widespread bacteria were observed in the brain of raxibacumab-treated animals, while bacteria in the brain of untreated control animals were often confined to blood vessels or the immediate perivascular space. However, untreated control animals had a greater incidence and/or severity of parenchymal organ lesions, mainly lymph nodes, liver, and spleen, than did raxibacumab-treated animals.

Study 866-002 entitled, "Blinded Re-read of Selected Slides and Tissues from the Study Evaluation of Raxibacumab Efficacy as Therapeutic Treatment against Inhalation Anthrax in the Cynomolgus Macaque" was a blinded re-rereading of the histopathology slides by EPL. This study demonstrated similar findings to those reported by Battelle. Table 5.1.1-6 below compares the findings in all the tissues.

Table 5.1.1-5 Histopathology findings, CNS in Monkeys

Group	Placebo		Raxibacumab 20 mg/kg		Raxibacumab 40 mg/kg	
Number in Group	**12**		**14**		**14**	
Mortality	**100%**		**50%**		**36%**	
Sex	**M**	**F**	**M**	**F**	**M**	**F**
#Dead	**6**	**6**	**4**	**3**	**2**	**3**
Bacteria (Average Severity)	6 (1.2)	5 (1.2)	3 (2.3)	2 (2.3)	2 (2.0)	3 (2.0)
Fibrinoneutrophilic Inflammation (Average Severity)	0 (0)	1 (0.5)	3 (2.3)	3 (3.0)	1 (2.0)	1 (1.0)
Hemorrhage (Average Severity)	1 (0.2)	1 (0.5)	3 (2.3)	3 (3.0)	1 (2.0)	2 (2.0)
Neuropil Necrosis (Average Severity)	0 (0)	1 (0.3)	1 (0.3)	2 (1.3)	1 (1.0)	0 (0)

Severity is defined as 1=minimal, 2=mild, 3=moderate, 4=severe
(Adapted from HGS' BLA submission Study No. 901 -G005829, p.28)

Table 5.1.1-6 Histopathology Findings in Monkeys, Organs Examined

Incidence (Severity[1]) Among Non-Survivors							
Battelle				EPL			
Tissue/Observation	Placebo (n = 12)	20 mg/kg Raxibacumab (n = 7)	40 mg/kg Raxibacumab (n = 5)	Tissue/Observation	Placebo (n = 12)	20 mg/kg Raxibacumab (n = 7)	40 mg/kg Raxibacumab (n = 5)
Lymph node, bronchial	(n = 8)	(n = 3)	(n = 3)	Lymph node, bronchial	(n = 8)	(n = 3)	(n = 3)
Bacteria	8 (1.3)	2 (0.7)	1 (0.5)	Bacteria	8 (1.6)	3 (1.3)	1 (0.5)
Hemorrhage	5 (1.5)	1 (0.3)	1 (0.5)	Hemorrhage	5 (1.4)	1 (0.7)	1 (0.5)
Inflammation	1 (0.3)	1 (0.3)	0	Inflammation	1 (0.3)	0	0
Necrosis	8 (2.1)	3 (1.0)	0	Necrosis	8 (2.4)	1 (0.3)	1 (0.5)
Lymph node, mediastinal	(n = 11)			Lymph node, mediastinal	(n = 11)		
Bacteria	11 (1.4)	5 (0.9)	2 (0.4)	Bacteria	10 (1.4)	4 (0.6)	2 (0.6)
Hemorrhage	6 (1.1)	1 (0.1)	2 (0.4)	Hemorrhage	4 (0.8)	0	1 (0.2)
Inflammation	0	0	0	Inflammation	1 (0.1)	0	0
Necrosis	10 (1.8)	4 (0.9)	4 (1.0)	Necrosis	10 (2.2)	5 (1.4)	0
Lung				Lung			
Bacteria	11 (2.2)	3 (0.4)	4 (1.2)	Bacteria	11 (2.5)	0	2 (0.8)
Hemorrhage	3 (0.4)	1 (0.1)	0	Hemorrhage	1 (0.3)	0	1 (0.1)
Inflammation	6 (0.6)	2 (0.3)	1 (0.2)	Inflammation (chronic active)	4 (0.4)	4 (0.6)	1 (0.2)
Kidney				Kidney			
Bacteria	11 (1.8)	3 (0.4)	4 (0.6)	Bacteria	10 (0.8)	1 (0.1)	3 (0.8)
Hemorrhage	0	0	0	Hemorrhage (tubular)	1 (0.1)	0	1 (0.1)
Inflammation	0	1 (0.1)	0	Inflammation	0	1 (0.1)	0
Necrosis	0	0	0	Necrosis	-	-	-

Liver				Liver			
Bacteria	11 (1.76)	3 (0.4)	3 (0.6)	Bacteria	8 (1.8)	1 (0.1)	2 (0.4)
Hemorrhage	-	-	-	Hemorrhage	1 (0.3)	0	0
Inflammation	-	-	-	Inflammation	1 (0.2)	1 (0.1)	0
Necrosis	2 (0.3)	1 (0.1)	0	Necrosis	5 (0.6)	3 (0.7)	0
Spleen				Spleen			
Bacteria	10 (3.9)	4 (0.9)	3 (1.6)	Bacteria	9 (2.8)	2 (0.3)	3 (1.2)
Hemorrhage	0	0	0	Hemorrhage	7 (1.2)	1 (0.3)	3 (0.8)
Inflammation	0	0	0	Inflammation (acute)	4 (0.4)	2 (0.9)	4 (1.6)
Necrosis	11 (1.9)	5 (0.9)	5 (1.4)	Necrosis	12 (3.0)	7 (2.0)	4 (2.2)
Fibrin exudation	7 (0.8)	3 (0.6)	2 (0.6)	Fibrin accumulation	4 (0.4)	0	6 (1.4)
Brain				Brain			
Bacteria	11 (1.2)	5 (2.3)	5 (2.0)	Bacteria	9 (1.1)	6 (2.9)	5 (2.2)
Hemorrhage	2 (0.3)	6 (2.6)	4 (2.0)	Hemorrhage	4 (0.5)	7 (2.6)	4 (2.2)
Inflammation	1 (0.3)	6 (2.6)	3 (1.4)	Inflammation	0	1 (0.4)	0
				Inflammation (chronic active)	1 (0.3)	4 (1.7)	2 (1.4)
Necrosis	1 (0.2)	3 (0.7)	2 (0.4)	Necrosis	0	5 (0.7)	0

[1] Severity is measured on a scale of 1 to 4, where 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.

(Adapted from HGS' BLA Submission, Summary of Clinical Pharmacology Studies, p. 163-164)

CNS Findings (Section 7.4) of this document contains a detailed discussion of the pathologic findings in the context of time to bacteremia, time from bacteremia to treatment, time from treatment to death, and time from challenge to death.

5.1.2 New Zealand White Rabbit

Title of Study: 682-G005758: Evaluation of Raxibacumab Efficacy as Therapeutic Treatment Against Inhalation Anthrax in the Rabbit Model

Objectives

- To evaluate the efficacy of raxibacumab when administered as a therapeutic treatment against lethality upon appearance of clinical symptoms due to inhalation exposure to *B. anthracis* in New Zealand White (NZW) rabbits.
- To determine the PK of raxibacumab following a single IV raxibacumab dose and the kinetics of *B. anthracis* PA in rabbits with inhalation anthrax.

Study Design, and Methods

This study was designed as an open-label, single center, randomized, placebo controlled dose-ranging study of raxibacumab given as a single IV bolus at either 20 or 40mg/kg dose or placebo to NZW rabbits to evaluate the therapeutic efficacy of a single IV dose of raxibacumab in anthrax spore inhalation challenged rabbits experiencing the symptoms of inhalation anthrax. The study was conducted at BBRC. The primary objective was to evaluate raxibacumab efficacy as therapeutic treatment against inhalation anthrax induced lethality in a NZW rabbit model of established inhalational anthrax. Survival in the bacteremic population was the primary analytic endpoint in the FDA analysis, as had been discussed with HGS, whose protocol prespecified primary analysis in the ITT population. Assuming raxibacumab efficacy of 50%, with three cohorts of 18 animals per group, the study provides 80% power at overall significance level of 0.05 to detect an absolute difference of 45% or more in 14 day survival in one of the raxibacumab treatment groups (20 or 40 mg/kg). Animals received the following interventions when disease was identified (trigger) by bacteremia, or either PA toxemia and temperature

elevation of ≥2˚F. The latter criteria correlate with bacteremia development in the natural history study in NZW rabbits.

Table 5.1.2-1 illustrates the treatment groups. Raxibacumab was administered as a bolus infusion. The animal's disposition is illustrated in Figure 5.1.2-1.

Table 5.1.2-1 Treatment Groups

		Raxibacumab Treatment		
Group	**# of Animals**	**Dose (mg/kg)**	**Dose Schedule and Route**	**Treatment Point Post-Challenge**
1 (Control Group)	18	Raxibacumab buffer [a]	Single IV	Individual times will be based on serum PA levels or body temperature [b]
2	18	20 Raxibacumab	Single IV	Individual times will be based on serum PA levels or body temperature [b]
3	18	40 Raxibacumab	Single IV	Individual times will be based on serum PA levels or body temperature [b]

a Dose equivalent in ml/kg volume to Group 3.
b Each individual rabbit in groups 1- 3 will receive assigned treatment immediately upon either its first positive PA result, or its first two consecutive time points of a body temperature 2 or more degrees F higher than the baseline average (whichever occurs first).

Study animals were randomized by dose group and gender, and aerosol challenged with the *B. anthracis* Ames strain at 200 x LD50 at Day 0. Temperature was measured every hour from 12h to 72h post-challenge. Blood samples were collected for detection of PA (ECL and ELISA), culture, PCR for *B. anthracis*, and CBC/CRP every 4 hours from 12h to 72h post-challenge. Intervention was to occur based on the trigger for intervention: positive PA toxemia by ECL or a 2º F sustained temperature increase over baseline. Clinical observations were recorded every 12h and animals were euthanized at day 14 or if found moribund. Necropsy and histopathology were conducted on all euthanized for moribundity and all dead animals.

Figure 5.1.2-1 Animal's Disposition- NZW Rabbits

**Animal L08147 was bacteremic by culture 1.4hours prior to treatment with raxibacumab 40mg/kg; however, sample drawn immediately prior to raxibacumab administration did not grow bacteria. Blood cultures remained negative for the remainder of the study period. Animal was febrile for 5 hours prior to treatment and remained febrile for additional 17 hours after treatment. Animal's PA levels by ELISA at the time of treatment were at lower limit of detection. This animal was considered to be bacteremic prior to treatment administration by FDA*

Efficacy Results

The efficacy described below in Table 5.1.2-2 is based on the FDA statistical analyses of the population of animals that were identified by clinical/microbiology reviewers as having inhalational anthrax by the presence of bacteremia prior to treatment. The results indicate that only the 40 mg/kg raxibacumab dose achieved a statistically significant mortality difference compared to placebo.

Table 5.1.2-2 Primary Efficacy Results in NZW Rabbits (Survival at Day 14)

Population	Treatment	N	No. of Survivors (%)	P-value*	95% CI** of Raxibacumab-placebo (%)	97.5% CI** of Raxibacumab – placebo (%)
HGS ITT	Placebo	17	0 (0.0%)			
	20 mg/kg Raxibacumab	18	5 (27.8%)	0.0455	(6.6, 52.5)	(1.4, 54.5)
	40 mg/kg Raxibacumab	18	8 (44.4%)	0.0029	(21.3, 66.7)	(16.1, 69.6)
FDA primary	Placebo	13	(0.0%)			
	20 mg/kg Raxibacumab	16	4 (25.0%)	0.1067	(-2.2, 50.9)	(-7.8, 53.4)
	40 mg/kg Raxibacumab	17	6 (35.3%)	0.0237	(7.3, 59.6)	(2.2, 62.3)

*two-sided Fisher's exact test for comparisons between the treatment and placebo

** CIs are exact confidence intervals.

The FDA exploratory analyses showed a similar trend in survival with the 40mg/kg dose when disease was defined by the screening and quantitative toxin assays (Table 5.1.2-3).

Table 5.1.2-3 Primary Efficacy Endpoint Sensitivity Analyses

Study population	Placebo	Raxibacumab 20mg/kg	Raxibacumab 40mg/kg
As Treated Toxemic Animals (Screening Assay*)			
	N=10	**N=8**	**N=11**
Survival, n (%)	**0**	**1 (12.5)**	**4 (36.4)**
As Treated Toxemic Animals (Quantitative Assay)**			
	N=13	**N=17**	**N=16**
Survival, n (%)	0	5 (29.4)	6 (37.5)
As Treated Toxemic (Quantitative Assay) and Bacteremic Animals			
	N=12	**N=16**	**N=15**
Survival, n (%)	0	4 (25)	5 (33.3)

* both plate and sample had to pass quality controls for the results to be considered positive (7 additional animals found to be positive for PA by screening assay, but failed plate quality control, therefore were excluded from the analyses. Also, 2 additional animals found to be PA positive by screening assay only at baseline, but not after challenge were excluded from the above analyses.

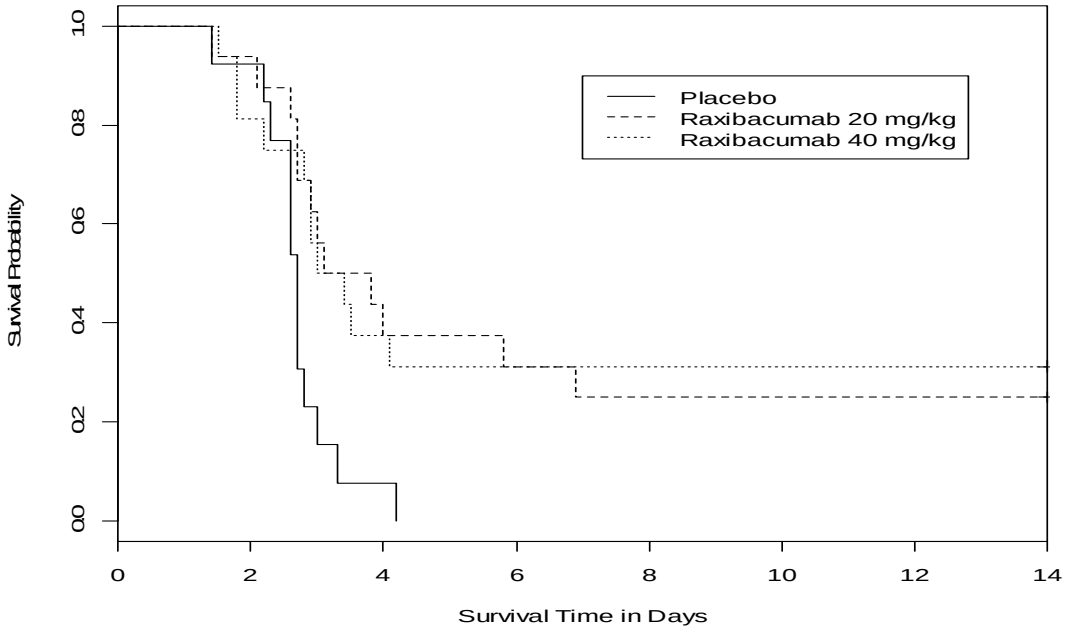
**3 animals (2 placebo and 1 raxibacumab 20mg/kg) had positive PA at the time of pre-study screening, but went on to be challenged and continued to be positive at all remaining timepoints, and eventually succumbed to death from anthrax. These animals were included in the above analyses. If they were to be excluded, the results would look as follows:

- As treated toxemic animals (quantitative assay) placebo 0/11, raxibacumab 20mg/kg 5/16 (31.3%)
- As treated toxemic (quantitative assay) and bacteremic animals placebo 0/11, raxibacumab 20mg/kg 4/15 (26.7%)

Secondary Efficacy Endpoint

The secondary efficacy endpoint was survival time defined as the time from the beginning of spore challenge to death during the 14-day study period. The graph of the Kaplan-Meier survival curves for the three treatment groups of rabbits is presented in Figure 5.1.2-2 below for the FDA primary analysis population. The median survival times were 2.7 days in the placebo group, 3.5 days in the raxibacumab 20 mg/kg group and 3.2 days in the raxibacumab 40 mg/kg group. There were statistically significant differences in terms of survival time among the three groups (log rank test, p=0.0125).

Figure 5.1.2-2 Survival Probability of Rabbits in FDA Primary Analysis Population



Laboratory Safety Results

CBC and Differential

Hematologic parameters such as neutrophilia and lymphopenia were observed in >50% of the animals prior to treatment. In survivors lymphopenia and thromocytosis were most prominent features on hemogram in the recovery phase.

Necropsy and Histology

The animals that succumbed to disease or were sacrificed due to moribundity were necropsized. The internal organs were examined for gross pathology and then sections were examined microscopically. The necropsy and histopathology readings were initially performed by the pathologist at Battelle in a blinded fashion. Upon Division's request, the organs and histopathology slides were re-examined and read by an independent peer review pathology panel (EPL), and both are described in Table 5.1.2-4.

Table 5.1.2-4 Histopathology Findings among NZW Rabbit Non-survivors in Study 682-G005758 by Battelle and Independent Pathology Review Panel (EPL)

Incidence (Severity[1]) Among Non-Survivors							
	Battelle				EPL		
Tissue/Observation	Placebo (n = 16)	20 mg/kg Raxibacumab (n = 12)	40 mg/kg Raxibacumab (n = 11)	Tissue/Observation	Placebo (n = 16)	20 mg/kg Raxibacumab (n = 12)	40 mg/kg Raxibacumab (n = 11)
Lymph node, bronchial				Lymph node, bronchial			
Bacteria	15 (3.0)	3 (0.8)	5 (1.2)	Bacteria	13 (2.7)	4 (0.9)	5 (1.1)
Hemorrhage	12 (1.8)	10 (2.0)	6 (1.6)	Hemorrhage	11 (1.6)	9 (1.7)	7 (1.9)
Inflammation	15 (3.0)	12 (3.2)	11 (2.5)	Inflammation	13 (2.1)	3 (0.8)	6 (1.5)
Necrosis	16 (3.4)	12 (2.9)	9 (2.5)	Necrosis	15 (3.2)	11 (2.8)	11 (3.1)
Lymph node, mediastinal				Lymph node, mediastinal			
Bacteria	13 (3.1)	3 (0.8)	5 (1.3)	Bacteria	15 (3.4)	3 (0.8)	4 (1.1)
Hemorrhage	14 (1.9)	10 (2.0)	6 (1.8)	Hemorrhage	12 (1.7)	10 (1.8)	6 (1.8)
Inflammation	12 (2.6)	12 (2.3)	10 (2.6)	Inflammation	12 (2.3)	4 (0.9)	6 (1.1)
Necrosis	15 (3.1)	8 (2.0)	8 (2.5)	Necrosis	16 (3.4)	12 (2.6)	11 (2.8)
Lung				Lung		3 (0.3)	
Bacteria	15 (2.9)	2 (0.2)	1 (0.1)	Bacteria	15 (3.2)	0	1 (0.1)
Hemorrhage	5 (0.6)	1 (0.1)	0	Hemorrhage (alveolus)	4 (0.7)	7 (1.1)	1 (0.1)
Inflammation	9 (1.0)	7 (0.8)	7 (0.8)	Inflammation	16 (2.1)	0	6 (0.8)
Necrosis	1 (0.1)	0	0	Necrosis (vessels)	1 (0.1)		0
Kidney				Kidney			
Bacteria	15 (2.0)	4 (0.6)	3 (0.6)	Bacteria	15 (2.5)	4 (0.6)	4 (0.6)
Hemorrhage	7 (0.4)	3 (0.5)	2 (0.3)	Hemorrhage (tubular)	9 (0.6)	4 (0.3)	2 (0.4)
Inflammation	0	6 (0.8)	1 (0.2)	Inflammation	0	3 (0.5)	0
Necrosis	1 (0.1)	2 (0.3)	3 (0.4)	Necrosis (glomerular)	2 (0.1)	4 (0.3)	4 (0.4)
				Necrosis (tubular)	8 (0.67)	7 (0.8)	4 (0.7)
Liver				Liver			
Bacteria[2]	-	-	-	Bacteria	15 (1.4)	1 (0.1)	0
Hemorrhage	-	-	-	Hemorrhage	1 (0.1)	0	0
Inflammation	0	1 (0.1)	0	Inflammation	-	-	-
Necrosis	6 (0.8)	5 (0.7)	3 (0.7)	Necrosis (hepatocellular)	8 (1.1)	7 (0.8)	6 (1.2)
Spleen				Spleen			
Bacteria	15 (3.1)	2 (0.3)	1 (0.1)	Bacteria	13 (2.4)	1 (0.1)	0
Hemorrhage	-	-	-	Hemorrhage	7 (0.6)	3 (0.3)	4 (0.7)
Inflammation	7 (0.8)	4 (0.3)	4 (0.5)	Inflammation	1 (0.2)	1 (0.1)	3 (0.5)
Necrosis	8 (1.2)	2 (0.2)	1 (0.3)	Necrosis	17 (3.2)	12 (3.2)	11 (2.6)
Fibrin accumulation	13 (2.0)	9 (1.8)	8 (2.1)	Fibrin accumulation	14 (1.7)	8 (1.3)	7 (1.5)
Brain				Brain			
Bacteria	3 (0.3)	9 (2.2)	7 (1.5)	Bacteria	15 (1.1)	9 (1.8)	7 (1.7)
Hemorrhage	4 (0.5)	10 (1.9)	7 (1.7)	Hemorrhage	4 (0.4)	9 (1.2)	6 (1.4)
Inflammation	2 (0.2)	8 (1.3)	5 (1.2)	Inflammation	0	0	1 (0.1)
Necrosis	0	5 (0.7)	6 (1.0)	Necrosis	1 (0.1)	4 (0.5)	4 (0.6)

[1] Severity is measured on a scale of 1 to 4, where 1 = minimal, 2 = mild, 3 = moderate, and 4 = marked.

[2] In the reading of these slides, bacteria were only scored if it appeared in the liver cells, not if it was confined to vessels within the liver.

(Adapted from HGS' BLA submission, Clinical Summary, p.158-9)

Among rabbits that succumbed to anthrax, those that received raxibacumab had significantly less bacterial burden and pathologic changes evident in visceral tissues as compared to placebo animals. However, CNS pathology in non-surviving animals (demonstrated on necropsy/ histopathology) was more prominent in severity, extent and frequency in raxibacumab-treated animals. Bacteria aggregated in the intra- and peri-vascular areas, subarachnoid space, choroid plexus, and was accompanied by vasculitis and fibrinoid necrosis. These CNS changes were less frequent and less prominent in placebo treated animals. The **CNS Findings (Section 7.4)** of this

document contains a detailed discussion of the pathologic findings in the context of time to bacteremia, time from bacteremia to treatment, time from treatment to death, and time from challenge to death.

5.2 Efficacy of Raxibacumab and Antimicrobial in Animal Models of Inhalational Anthrax

In addition to conducting studies of raxibacumab versus placebo in monkeys and rabbits, HGS also conducted studies to test the efficacy of raxibacumab in combination with antimicrobial therapy in monkeys and in rabbits. The analysis populations for these studies were defined in the same way as for the raxibacumab versus placebo studies. The study design and outcome for each study are summarized below.

5.2.1 Cynomolgus Monkey

Study 789-G923702: "Evaluation of the Efficacy of Raxibacumab in Combination with Ciprofloxacin for Therapeutic Treatment in the Cynomolgus Monkey Inhalation Anthrax Model"

Objectives

- To evaluate the efficacy of raxibacumab when administered as a therapeutic agent in combination with ciprofloxacin against lethality due to inhalation exposure of *B. anthracis* in cynomolgus monkeys.
- To determine the PK of intragastric (IG) ciprofloxacin doses and of an IV raxibacumab dose when co-administered, as well as the kinetics of *B. anthracis* protective antigen (PA), in monkeys with inhalation anthrax.

Study Design

This was a parallel-group, double-blind, randomized, placebo-controlled study to evaluate the efficacy of raxibacumab in combination with ciprofloxacin as a therapeutic treatment in the cynomolgus monkey inhalation anthrax model. PA kinetics and raxibacumab and ciprofloxacin PK were also examined.

Methods

Forty (50% male, 50% female) juvenile (< 5 years of age) cynomolgus macaques (*Macaca fascicularis*) weighing between 2.0 to 6.0 kg at randomization were randomized into 3 treatment groups (see table 5.2.1-1 below), and randomly assigned to 1 of 3 aerosol challenge days and a challenge order.

Table 5.2.1-1 Treatment Groups

Group	N	Ciprofloxacin/Control	Raxibacumab/Control	Treatment Point
Group 1 (Control)	12	Sterile water IG	Raxibacumab buffer IV (1mL/kg)	Individual treatment times were based on serum PA levels as detected by ECL
Group 2 (Ciprofloxacin)	14	75 mg IG every 12h for 6 doses	Raxibacumab buffer IV (1mL/kg)	
Group 3 (Ciprofloxacin/ raxibacumab)	12	75 mg IG every 12h for 6 doses	Raxibacumab IV 40mg/kg after the first ciprofloxacin dose	

(Adapted from HGS' BLA submission, p.29)

The study was conducted at BBRC. On Day 0, monkeys were aerosol challenged with a targeted 200 x LD50 [1.24 x 107 spores] dose of *B. anthracis* spores (Ames strain) aerosolized by a Collison nebulizer and delivered via a head-only inhalation exposure chamber.

Monkeys were observed every 6 hours beginning 24 hours post median challenge time and ending 192 hours (8 days) post median challenge time for clinical signs including, but not limited to, anorexia, lethargy, respiratory distress, moribundity, activity (recumbent, weak, or unresponsive), seizures, and other abnormal clinical observations, after which they were observed twice daily, or more often if there was any sign of distress.

Treatment with study agent was triggered upon detection of serum PA via the ECL screening assay or at 54 hours post-challenge. Ciprofloxacin (75 mg) or control material (sterile water for injection, WFI) was administered IG for 6 doses: initially once the criterion for treatment was met and then every (Q) 12 hours (± 1 hour) for 5 doses. In addition, a single IV bolus dose of raxibacumab (40 mg/kg) or raxibacumab buffer (1 mL/kg) was administered immediately after administration of the first ciprofloxacin dose. Within five minutes prior to treatment each monkey received a single 1 mg/kg intramuscular (IM) dose of diphenhydramine to parallel the treatment paradigm for humans in Phase 2/3 studies. Staff members administering study agents were blinded to study agent preparation to preclude introduction of bias into the study following treatment.

Monkeys surviving the post-challenge could be returned to HGS (if required) or donated following observation for an additional 60 days under BL-2 laboratory conditions for recrudescence. Gross necropsy and histopathology were performed on all monkeys that were found dead or were euthanized. Blood samples were collected for hematology and CRP, as well as to measure bacteremia by culture, serum PA levels, anti-PA and TNA levels, serum raxibacumab levels and ciprofloxacin levels.

PK analyses of raxibacumab concentration-time profiles for all raxibacumab dosed monkeys were conducted using population analysis techniques (mixed effect modeling), with the NONMEM software. Serum ciprofloxacin concentration-time profiles for the subjects were analyzed individually. The maximum serum ciprofloxacin concentration after the first dose (Cmax,1) was defined as the concentration measured 1.5 hours after the 1st dose, while the minimum serum drug concentration after the nth dose (Cmin,n) was defined as the concentration measured just prior to the subsequent dose, or for the 6th dose, at 12 hours after that dose.

Statistical Analysis
All statistical tests were to be 2-sided and performed at a significance level of 0.05.

Demographics and Anthrax Exposure
The treatment groups were comparable with respect to sex, weight, age at randomization, and anthrax spore challenge. The anthrax spore challenge by treatment group is shown in the table 5.2.1-2 below.

Table 5.2.1-2 Spore Challenge Exposure

	Placebo N=12	Ciprofloxacin N=14	Ciprofloxacin/ Raxibacumab N=14	All Groups N=40	P-value*
Anthrax exposure (x LD_{50})					0.0688
N	12	14	14	40	
Mean ± SD	228.0 ± 58.0	290.8 ± 97.5	301.5 ± 85.5	275.7 ± 87.0	
Median	212.5	254.0	321.8	248.7	
Range	166.1-382.0	168.0-450.0	146.0-409.5	146.0-450.0	

* P-value based on 1-way ANOVA for comparison among all treatment groups.
(Adapted from HGS' BLA submission, p.51)

The time to treatment for animals that were bacteremic at the time of treatment was 42.4±6.5 hours for the placebo animals (N=10), 39.1±8.0 hours for the ciprofloxacin treated animals (N=13), and 38.9±6.0 hours for the ciprofloxacin/raxibacumab treated animals (N=13). There were no statistically significant differences between the groups.

Efficacy Results

Primary Endpoint
The primary efficacy endpoint was survival at Day 28, defined as the percent of animals alive at Day 28. The efficacy described below in Table 5.2.1-3 is based on the HGS ITT statistical analysis and the FDA primary analysis of those animals that were bacteremic (as defined by positive blood culture) at the time of treatment.

Table 5.2.1-3 Primary Efficacy Analysis in Monkeys

Population	Treatment	N	No. of Survivors (%)*	95% CI** of Cipro/Raxi – Cipro (%)
Sponsor's ITT	Placebo	12	0 (0.0%)	
	Ciprofloxacin	14	14 (100%)	
	Cipro/Raxi	14	12 (85.7%)	(-42.8, 11.9)
FDA primary	Placebo	10	0 (0.0%)	
	Ciprofloxacin	13	13 (100%)	
	Cipro/Raxi	13	11 (84.6%)	(-45.5, 11.4)

*There is significant difference between each active group and placebo (all p-values <0.0001).
**CIs are exact confidence intervals for comparison between cipro/Raxi and Ciprofloxacin.

None of the placebo treated animals survived. One of the two non-survivors in the ciprofloxacin/raxibacumab group died from pneumonia related to a potential gavage error. The other non-survivor in the ciprofloxacin/raxibacumab group tested negative for bacteremia at death but had evidence of meningitis and CNS hemorrhage. One animal in the ciprofloxacin group died at 36 days due to left leg arterial thrombosis with inflammation and fibrosis. No anthrax bacteria were found in any tissue in this animal. One survivor in the ciprofloxacin group and two survivors in the ciprofloxacin/raxibacumab group tested positive for anti-PA antibodies at baseline. All survivors in the study tested negative for TNA at baseline and positive for both anti-PA antibodies and TNA on Day 28.

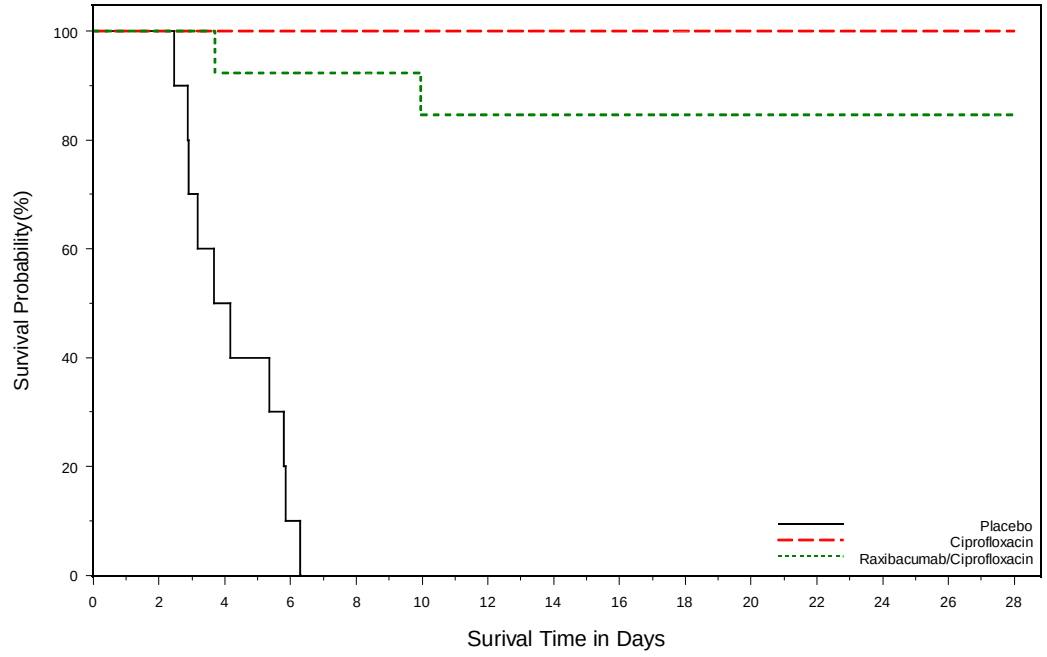
HGS concluded that both the ciprofloxacin and the ciprofloxacin/raxibacumab treatment groups achieved a statistically significant mortality difference compared to placebo. For the FDA primary analysis, two animals in the placebo group, one animal in the ciprofloxacin group, and one animal in the ciprofloxacin/raxibacumab group were excluded because they were not bacteremic at the time of treatment. After exclusion of these animals, the 28-day survival rates were 0%, 100%, and 84.6% in the placebo, ciprofloxacin, and ciprofloxacin/raxibacumab combination groups, respectively. There was no difference ($p=0.222$) in survival rates between the ciprofloxacin and ciprofloxacin/raxibacumab combination groups (-15.4%, 95% CI [-45.5%, 11.4%].

Sensitivity analyses with respect to the primary efficacy endpoint were performed on several populations. The as-treated population was the same as the ITT since all the animals received the assigned treatment (one placebo animal [C25576] appears to have been given a single dose of ciprofloxacin based on PK data but received placebo throughout the majority of the ciprofloxacin dosing schedule). There were two monkeys (C24800 in the placebo group and C23064 in the ciprofloxacin group) which were not toxemic at or before treatment initiation and were hence excluded from the "toxemic at treatment analysis". One animal in the ciprofloxacin group died after the 28 day study period of an unrelated complication. Sensitivity analyses as well as analysis excluding the non-anthrax death did not alter the conclusions of the primary efficacy analyses. There was no statistical difference in survival rate at Day 28 between the ciprofloxacin and ciprofloxacin/raxibacumab, both of which maintained statistically significant survival benefit as compared to placebo.

Secondary Endpoint

The secondary efficacy endpoint was survival time from spore challenge to death during the study period. The median survival time in the placebo group was 4.2 days based on HGS' ITT and 3.9 days based on the FDA primary analysis (Figure 5.2.1-1). Median survival time could not be determined for the ciprofloxacin and ciprofloxacin/raxibacumab groups because the medians extended beyond 28 days.

Figure 5.2.1-1 Study 789-G923702: Survival Probability of Monkeys in FDA Primary Analysis Population



Safety

Necropsy and Histopathology

All of the animals in the placebo group, one animal in the ciprofloxacin group, and two animals in the ciprofloxacin/raxibacumab group died or were euthanized. Lesions at necropsy consistent with anthrax included adrenal gland discoloration (indicating the presence of bacteria); brain/meningeal red-stained accumulation, discoloration or foci (hemorrhage and inflammation); abdominal and/or thoracic cavity fluid (effusion); enlargement of axillary, bronchial, mandibular and/or mediastinal lymph nodes (edema, fibrin exudation, and hemorrhage); and skin or thymic fluid (edema). Microscopic findings consistent with anthrax were present in 13/15 (12 placebo treated animals and 1 ciprofloxacin/raxibacumab treated animal).

The brains for these 15 animals were examined. In the placebo group, 8/12 had no gross and no to level 1 bacteria with an average survival time of 99.1 hours. 2/12 had meningeal congestion and level 1 bacteria with an average survival time of 103.6 hours. 1/12 had discolored meninges, hemorrhage, and level 2 bacteria with a survival time of 100 hours. 1/12 had hemorrhagic meningitis with level 3 bacteria, hemorrhage and meningitis with a survival time of 128.5 hours (this animal received the single dose of ciprofloxacin). The animal in the ciprofloxacin treated group who died at 36 days had no CNS findings. Two animals in the ciprofloxacin/raxibacumab treated group died. One animal had evidence of pneumonia due to a gavage error and had no CNS findings. The second animal had evidence of hemorrhagic meningitis that affected the entire brain with level 3 bacteria, level 1 hemorrhage, and level 3 meningitis. This animal had a survival time of 238.7 hours.

5.2.2 New Zealand White Rabbit

Study 781-G923701: "Evaluating the efficacy of raxibacumab in combination with levofloxacin for treatment in the New Zealand White Rabbit inhalational anthrax model"

Objectives

• To evaluate the efficacy of raxibacumab when administered in combination with levofloxacin as a therapeutic treatment against lethality due to inhalation exposure to *B. anthracis* in NZW rabbits.

• To determine the PK of intragastric (IG) levofloxacin doses and of an IV raxibacumab dose when co-administered, as well as the kinetics of *B. anthracis* protective antigen (PA), in rabbits with inhalation anthrax.

Study Design

This was a parallel-group, randomized, double-blind, placebo-controlled GLP study to evaluate the efficacy of raxibacumab in combination with levofloxacin for therapeutic treatment in the NZW rabbit inhalational anthrax model. PA kinetics and raxibacumab and levofloxacin PK were also examined.

Methods

Sixty New Zealand White rabbits (*Oryctolagus cuniculus*) (Covance Research Products, Inc) weighing 2.97 to 4.02 kg at randomization were obtained for the study. Fifty-two rabbits were randomized into one group of 12 rabbits and two groups of 20 rabbits (each group approximately 50% male, 50% female) and assigned to 1 of 3 aerosol challenge days and a challenge order. The eight remaining rabbits were to serve as replacements.

Rabbits were to be aerosol challenged on Day 0 with a targeted 200x the median lethal dose (LD50) (1.24 x 107 spores) of *B. anthracis* (Ames strain) spores. Treatment was administered based on a positive plasma PA result via ECL screening assay or two consecutive timepoints of a body temperature 2 or more °F higher than the baseline average temperature, whichever was noted first. Beyond 36 hours postchallenge until 72 hours postchallenge, only temperature was used as a trigger for treatment. If an animal had not been treated by 72 hours postchallenge (negative for PA and did not meet the temperature criteria), the animal was to be treated after its last hourly temperature assessment.

The following three treatment groups were evaluated:

- Group 1 (X): Individual rabbits received sterile WFI (2 mL/kg) IG upon trigger symptom detection, immediately followed by a single IV dose of raxibacumab buffer (1 mL/kg), and then one dose of sterile WFI (2 mL/kg) at 24 and 48 hours after trigger symptom detection.

- Group 2 (Y): Individual rabbits received levofloxacin (50 mg/kg) IG upon trigger symptom detection, immediately followed by a single IV dose of raxibacumab buffer (1 mL/kg), and then one dose of levofloxacin (50 mg/kg) at 24 and 48 hours after trigger symptom detection.

- Group 3 (Z): Individual rabbits received levofloxacin (50 mg/kg) IG upon trigger symptom detection, immediately followed by a single IV dose of raxibacumab (40 mg/kg), and then one dose of levofloxacin (50 mg/kg) at 24 and 48 hours after trigger symptom detection.

Demographics and Anthrax Exposure

The treatment groups were comparable with regard to sex, weight, and age at randomization. One rabbit (K99234) in the levofloxacin group tested positive for anti-PA antibodies at baseline; the levels were just above the LLOD. All rabbits in the levofloxacin/raxibacumab group tested negative for anti-PA antibodies at baseline. All rabbits in the active treatment groups tested negative for toxin neutralization activity (TNA) at baseline. The extent of anthrax exposure was similar between groups, with no statistically significant difference in mean spore dose among the three treatment groups. The mean inhaled spore dose exceeded the targeted dose of 200x LD50 in all groups.

The groups were similar with respect to signs and symptoms around the time of treatment. There were no rabbits that were bacteremic but not toxemic at or before treatment initiation. The vast majority of rabbits in all groups (47/52, 90.4%) were toxemic and bacteremic at or before treatment initiation. The incidence of temperature increase at or before treatment across all groups was low (6/52, 11.5%), reflecting the predominance of PA toxemia as the treatment trigger symptom in the rabbit model.

Efficacy Results

Primary Endpoint

The primary efficacy endpoint was survival at Day 28, defined as the percent of animals alive at Day 28. In the FDA primary analysis, the 28-day survival rates were 0%, 95.0%, and 94.1% in the placebo, levofloxacin, and levofloxacin/raxibacumab combination groups, respectively (Table 5.2.2-1). There was no difference (p=0.947) in survival rates between the levofloxacin and levofloxacin/raxibacumab combination groups (-0.88%, 95% CI [-23.9%, 19.6%]).

None of the 12 rabbits in the placebo group survived. There was one death in the levofloxacin group and one death in the levofloxacin/raxibacumab group. The one non-survivor in the levofloxacin group (K99203) was a 3.3 kg male that received a spore dose of 283.03 x LD50. The animal became toxemic by 24.5 hours postchallenge, bacteremic by 27.3 hours postchallenge, and received its levofloxacin treatment 27.3 hours postchallenge triggered by PA detection. The animal was discovered moribund and was euthanized 11 days postchallenge. The one non-survivor in the levofloxacin/raxibacumab group (K99246) was a 3.6 kg female that received a spore dose of 369.35 x LD50. The animal became toxemic and bacteremic by 20 hours postchallenge, and received its levofloxacin/raxibacumab treatment 23.2 hours postchallenge triggered by PA detection. This animal died as the result of a dosing accident (inadvertent intratracheal gavage of study agent).

Table 5.2.2-1: Survival at Day 28 in the ITT and FDA Primary Populations for NZW Rabbits

Population	Treatment	N	No. of Survivors (%)*	95% CI** of Levo/Raxi – Levo (%)
Sponsor's ITT	Placebo	12	0 (0.0%)	
	Levofloxacin	20	19 (95.0%)	
	Levo/Raxi	20	19 (95.0%)	(-20.4, 20.4)
FDA primary	Placebo	10	0 (0.0%)	
	Levofloxacin	20	19 (95.0%)	
	Levo/Raxi	17	16 (94.1%)	(-23.9, 19.6)

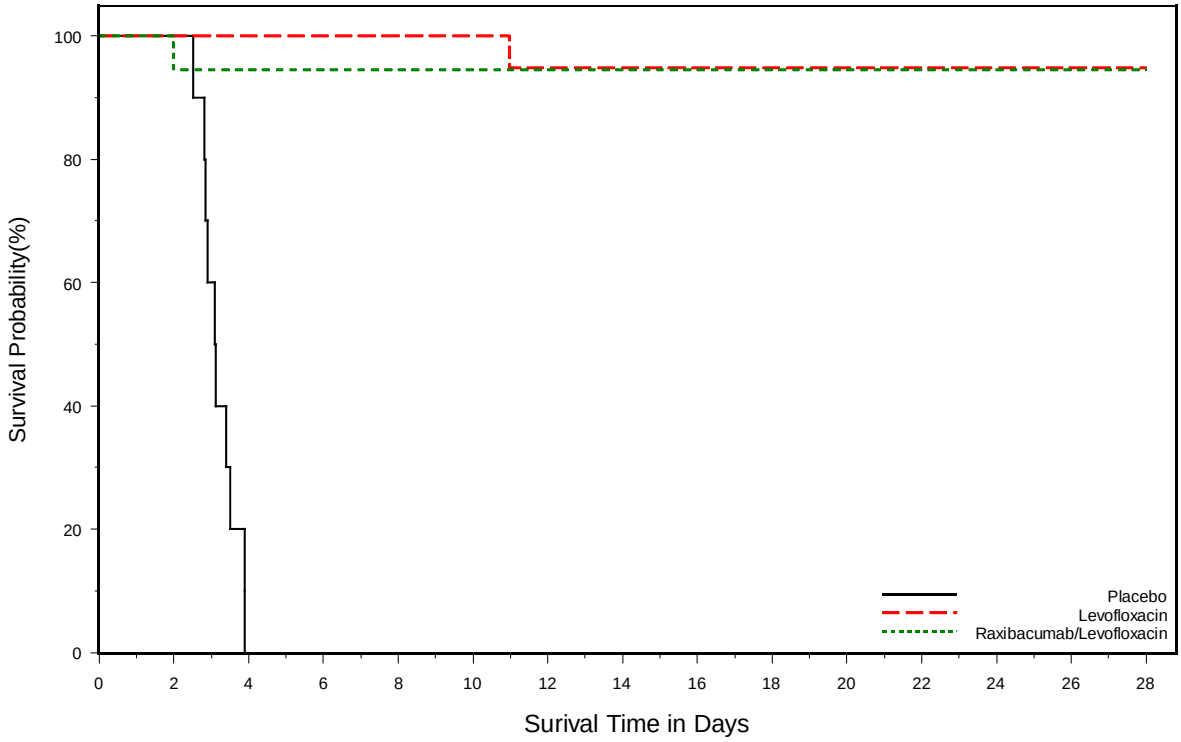
*There is significant difference between each active group and placebo (all p-values <0.0001).
**CIs are exact confidence intervals for comparison between levo/Raxi and levofloxacin.

Sensitivity analyses with respect to the primary efficacy endpoint were performed on several populations. One animal (K99251) was randomized to the Levo/Raxi group but received levofloxacin according to its PK data. This animal was included in the levofloxacin group for the as-treated analysis. There were 3 rabbits (K99254, K99202, and K99224) which were not toxemic at or before treatment initiation and were hence excluded from the toxemic at treatment analysis. One animal in the levofloxacin/raxibacumab group (K99246) died of dosing accident at 1.9 days post challenge. Sensitivity analyses as well as analysis excluding the non-anthrax death did not alter the conclusions of the primary efficacy analyses. There was no statistical difference in survival rate at Day 28 between the levofloxacin and levofloxacin/raxibacumab, both of which maintained statistically significant survival benefit as compared to placebo.

Secondary Endpoint

The secondary efficacy endpoint was survival time, defined as the time from the beginning of spore challenge to death during the 28-day postchallenge period. For animals that were alive at the end of the 28-day postchallenge period, survival times were to be censored on the date of study completion (672 hours). As shown in the Figure 5.2.2-1 below, survival time was significantly longer in the levofloxacin group ($p < 0.0001$) and the levofloxacin/raxibacumab group ($p < 0.0001$) relative to the placebo group. The difference in survival times between the 2 active treatment groups was not statistically significant ($p = 0.9855$ as determined by log-rank test). The median survival time in the placebo group was 78.5 hours, median survival time could not be determined for the levofloxacin and levofloxacin/raxibacumab groups because the medians extended beyond 28 days.

Figure 5.2.2-1 Study 781-G923701: Survival Probability of Rabbits in FDA Primary Analysis Population



Safety

Necropsy and Histopathology
All 52 animals, survivors and non-survivors, had their tissues examined microscopically. Gross lesions found in rabbits which died prior to study termination included enlargement, discoloration and/or foci of the adrenal glands, appendix, brain, lung and multiple lymph nodes; fluid (effusion) in the pericardial and thoracic cavities, and fluid/thickening (edema) of the skin and thymus. These correlated histologically with necrosis, inflammation, hemorrhage, edema and the visualization of anthrax bacteria. In contrast, gross lesions found in rabbits surviving to study termination were determined to be unrelated to anthrax infection.

Microscopic findings consistent with anthrax were present in all rabbits dying spontaneously or becoming moribund following anthrax challenge except for animal K99246, which was not bacteremic at death. None of the rabbits in the levofloxacin and levofloxacin/raxibacumab treatment groups had brain lesions on microscopic examination.

Please refer to the **CNS Findings (Section 7.4)** of this document for the discussion on CNS findings and conclusions. Exploratory analyses of various time elements for Study 781-G92370 were performed in the FDA Primary population and were limited by the few number of deaths (two) in the active treatment groups. Furthermore, if non-anthrax deaths are excluded, which is the most appropriate consideration for these analyses, this leaves only one anthrax death in the levofloxacin group. The mean times from treatment to death, survival time, and bacteremia to death were longer for the one animal that died in the levofloxacin treatment group compared to the animals in the placebo group.

6. Clinical Pharmacology

6.1 Interspecies Comparison of Raxibacumab Pharmacokinetics

To address the sufficiency of the clinical pharmacology data to support the use of a 40 mg/kg raxibacumab dose for therapeutic treatment of inhalation anthrax, measures of exposure (serum concentrations, Cmax, and AUC) were compared across humans, monkeys, and rabbits receiving single IV doses of raxibacumab. Pharmacokinetic information for raxibacumab (manufactured by the M11 to-be-marketed process) following intravenous administration was evaluated in humans, monkeys and rabbits in the following studies were used for purposes of interspecies comparison:

- Study HGS1021-C1064: an open-label study designed to determine the effect of co-administration of raxibacumab on PO administered ciprofloxacin PK and characterize the effect of co-administration of PO and IV administered ciprofloxacin on raxibacumab PK in healthy human subjects.
- Study 724-G005829: an animal efficacy study designed to evaluate raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the monkey model; this study included an evaluation of the PK of raxibacumab and the kinetics of *Bacillus anthracis* PA following a single IV raxibacumab dose in monkeys with inhalation anthrax (Pivotal Monkey Efficacy Study).
- Study 682-G005758: an animal efficacy study designed to evaluate raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the rabbit model; this study included an evaluation of the PK of raxibacumab and the kinetics of *Bacillus anthracis* PA following a single IV raxibacumab dose in rabbits with inhalation anthrax (Pivotal Rabbit Efficacy Study).

Serum concentration-time profiles for raxibacumab following single intravenous administration of 40 mg/kg in healthy, male and female subjects, monkeys with inhalation anthrax, and rabbits with inhalation anthrax are presented in Figure 6.1-1. Pharmacokinetic parameters for raxibacumab following single intravenous administration of 40 mg/kg in healthy, male and female subjects, monkeys with inhalation anthrax, and rabbits with inhalation anthrax are summarized in Table 6.1-1.

Following single intravenous administration of raxibacumab 40 mg/kg in healthy, male and female human subjects, raxibacumab appeared to distribute to tissues; mean Vss were greater than plasma volume, ranging between 65 to 72 mL/kg. Serum concentration-time profiles for raxibacumab suggest biphasic elimination with a mean terminal phase elimination half-life (t1/2,z) range from 20 to 22 days. Mean clearance (CL) ranged from 2.6 to 3.0 mL/day/kg among the dose groups studied. CL values were much smaller than the glomerular filtration rate indicating that there is virtually no renal clearance of raxibacumab.

Serum raxibacumab concentrations in monkeys administered raxibacumab were best fit to a two-compartment model with 1st-order elimination. The lack of difference in PK between treatment groups is consistent with linear PK over the dose range studied. Following IV raxibacumab administration, V1 was approximately 53 and 40 mL/kg for a 3 kg male and female animal, respectively, similar to plasma volume. The steady-state volume of distribution (Vss)

was nearly 2-fold greater than V1, suggesting that although distribution of raxibacumab may initially be restricted to the plasma volume, raxibacumab does subsequently distribute to tissues. The disappearance of raxibacumab from serum is multiphasic. The mean CL of raxibacumab in the monkey was much less than the glomerular filtration rate (2995 mL/day/kg), indicating that, similar to humans, there is virtually no renal clearance of raxibacumab. Inter-individual variability in raxibacumab PK was low, with CV% of 26% or less for the primary PK parameters. V1 and CLD2 are dependent on sex, with females having smaller values for each parameter than males.

Similar to monkeys, serum raxibacumab concentrations in rabbits were best fit a two-compartment model with 1st-order elimination. The lack of difference in PK between treatment groups is consistent with linear PK over the dose range studied. Following IV raxibacumab administration, V1 was the same as the plasma volume. The steady-state volume of distribution (Vss) is about 43% greater than V1, suggesting that although distribution of raxibacumab may initially be restricted to the plasma volume, raxibacumab does subsequently distribute to tissues. Similar to humans and monkeys, mean CL of raxibacumab was much smaller than the glomerular filtration rate (4493 mL/day/kg) indicating that there is virtually no renal clearance of raxibacumab. Inter-individual variability in raxibacumab PK was low, with CV% of 27% or less for the primary PK parameters.

Figure 6.1-1. **Mean (SD) Serum Concentration-Time Profiles for Raxibacumab Following Single Intravenous Administration of 40 mg/kg in Healthy, Male and Female Subjects, Monkeys with Inhalation Anthrax, and Rabbits with Inhalation Anthrax**

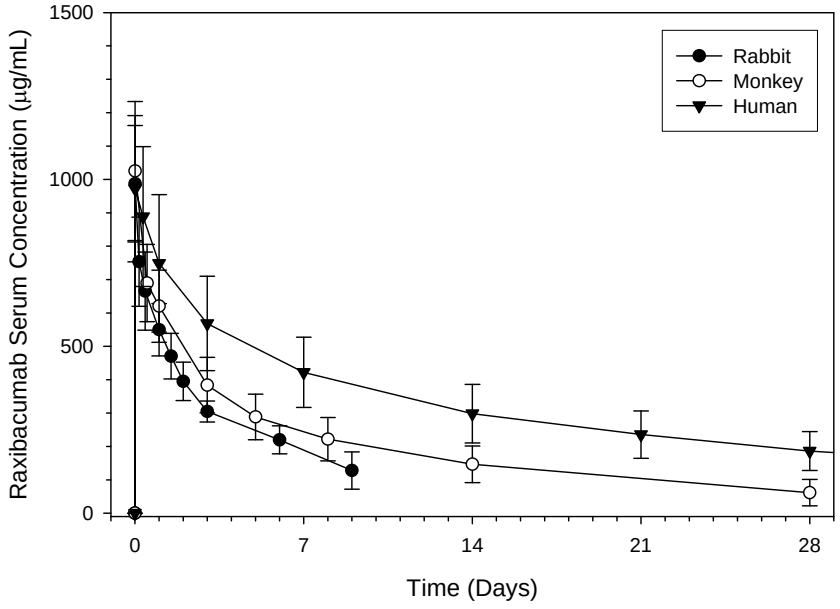


Table 6.1-1. Pharmacokinetic Parameters for Raxibacumab Following Single Intravenous Administration in Healthy, Male and Female Subjects, Monkeys with Inhalation Anthrax, and Rabbits with Inhalation Anthrax

Species	Dose Group	N	Cmax (µg/ml)	AUCinf (µg·day/ml)	Half life (days)	CL (ml/day/kg)	Vss (ml/kg)
Rabbit	**20 mg/kg**	17	459.9 ± 57.8 (342.5 - 544.8)	1719.1 ± 223.5 (1380.4 - 2196.7)	3.97 ± 0.73 (2.63 – 5.44)	11.6 ± 1.71 (9.10 – 15.5)	63.11 ± 7.91 (52.9 – 82.0)
Rabbit	**40 mg/kg**	19	918.8 ± 124.0 (623.8 – 1166.0)	3424.0 ± 464.1 (2541.4 – 3348.7)	4.10 ± 0.85 (2.99 – 6.10)	11.7 ± 1.81 (8.83 – 15.23)	63.8 ± 8.48 (51.9 – 87.9)
Monkey	**20 mg/kg**	14	490.5 ± 87.7 (275.6 – 613.2)	3575.9 ± 827.9 (2499.0 – 5240.4)	11.1 ± 1.94 (7.95 – 14.61)	5.85 ± 1.29 (3.80 – 8.00)	84.2 ± 10.3 (73.8 – 110.3)
Monkey	**40 mg/kg**	14	989.8 ± 170.1 (788.8 – 1422.9)	6490.6 ± 2095.5 (3899.4 – 11934.5)	10.1 ± 2.35 (5.98 – 14.3)	6.61 ± 1.90 (3.30 – 10.2)	82.8 ± 9.10 (64.5 – 93.3)
Human Group 1	**40 mg/kg + cipro PO**	27[a]	1143.3 ± 169.5 (833.6 – 1517.8)	14871.9 ± 3821.1 (5494.5 – 21116.6)	19.8 ± 8.18 (4.27 – 45.8)	2.99 ± 1.38 (1.85 – 7.30)	64.9 ± 11.9 (44.1 – 99.8)
Human Group 2	**40 mg/kg**	27[b]	1020.3 ± 140.6 (766.2 – 1293.7)	15845.8 ± 4333.5 (7614.9 – 25464.6)	20.6 ± 6.54 (5.93 – 32.3)	2.73 ± 0.84 (1.57 – 5.24)	69.7 ± 13.7 (45.6 – 106.7)
Human Group 3	**40 mg/kg + cipro IV/PO**	28	1047.8 ± 180.3 (772.5 – 1458.4)	16349.3 ± 4255.7 (7117.5 – 27465.2)	21.5 ± 8.92 (6.53 – 42.9)	2.63 ± 0.82 (1.46 – 5.62)	67.2 ± 12.6 (47.6 – 93.2)

Data presented represents mean ± one standard deviation and (minimum – maximum)

[a] Subjects US003-000006 and US003-000028 excluded for receiving only partial doses of raxibacumab. Subject US003-00029 excluded for PK profile uncharacteristic of IV administration.

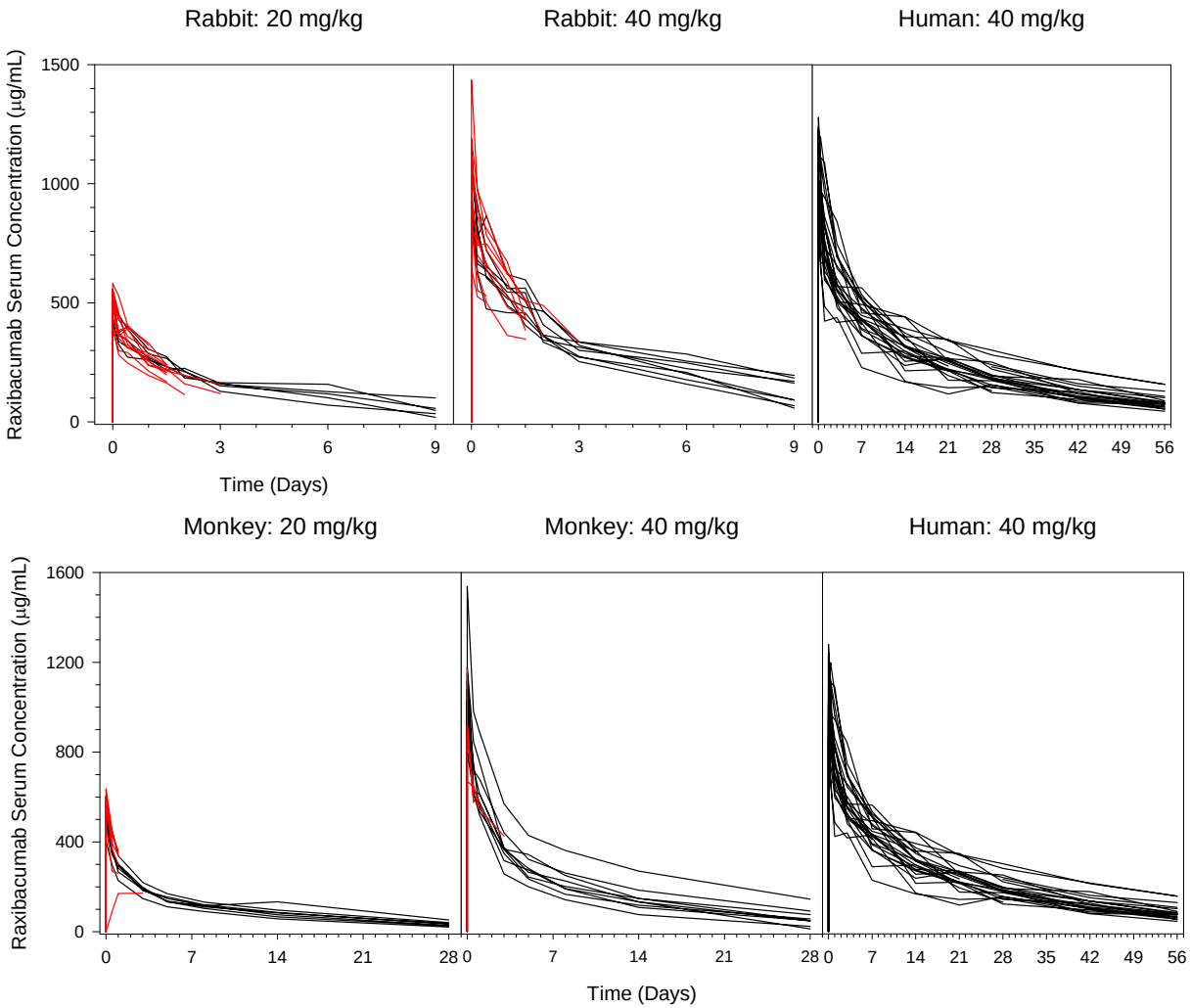
[b] Subject US003-000002 excluded for receiving only a partial dose of raxibacumab.

Individual serum concentration-time profiles for raxibacumab following single intravenous administration of 40 mg/kg in healthy, male and female subjects and 20 mg/kg and 40 mg/kg in monkeys and rabbits with inhalation anthrax are presented in Figure 6.1-2. The range of raxibacumab serum concentrations observed in both monkeys and rabbits following single 20 mg/kg and 40 mg/kg IV doses are compared to individual human serum concentration-time profiles following a single 40 mg/kg dose in Figures 6.1-3 and 6.1-4. Point plots of individual Cmax and AUCinf values following single intravenous administration of 40 mg/kg in healthy, male and female subjects and 20 mg/kg and 40 mg/kg in monkeys and rabbits with inhalation anthrax are illustrated in Figure 6.1-5.

Serum concentrations of raxibacumab following a single IV dose of 40 mg/kg alone in humans fell within or exceeded the range of concentrations observed in rabbits and monkeys receiving single 40 mg/kg IV doses, except for two subjects at the 24-hour sampling time point. Mean raxibacumab Cmax in humans following a single 40 mg/kg IV dose was similar to or greater than mean Cmax values in monkeys and rabbits. Individual raxibacumab Cmax values in humans following a single IV dose of 40 mg/kg alone fell within the range of Cmax values observed in rabbits. All but one Cmax in humans fell within the range of values observed in the monkeys. Mean raxibacumab AUCinf in humans following a single 40 mg/kg IV dose was 2.4- and 4.6-fold that of the mean Cmax values in monkeys and rabbits, respectively. Individual raxibacumab AUCinf values in humans following a single IV dose of 40 mg/kg alone fell within or exceeded the range of AUCinf values observed in rabbits and monkeys. Clearance of raxibacumab was significantly slower in humans as compared to rabbits, by a factor of approximately 5, and in monkeys, by a factor of approximately 3. Thus, the half-life of raxibacumab was substantially longer in humans compared to mean half-lives observed in monkeys and rabbits (20.6 ± 6.5 days versus 10.1 ± 2.4 days and 4.1 ± 0.85 days, respectively). Variability in Cmax was similar across species; %CV values ranged between approximately 13 to 17%. Variability in AUCinf was wider, ranging between 13 and 32% across species.

In summary, humans achieve similar to or greater exposure to raxibacumab following a single 40 mg/kg IV dose compared to rabbits and monkeys receiving the same dose. Humans achieve much greater exposure to raxibacumab following a single 40 mg/kg IV dose compared to rabbits and monkeys receiving a 20 mg/kg dose.

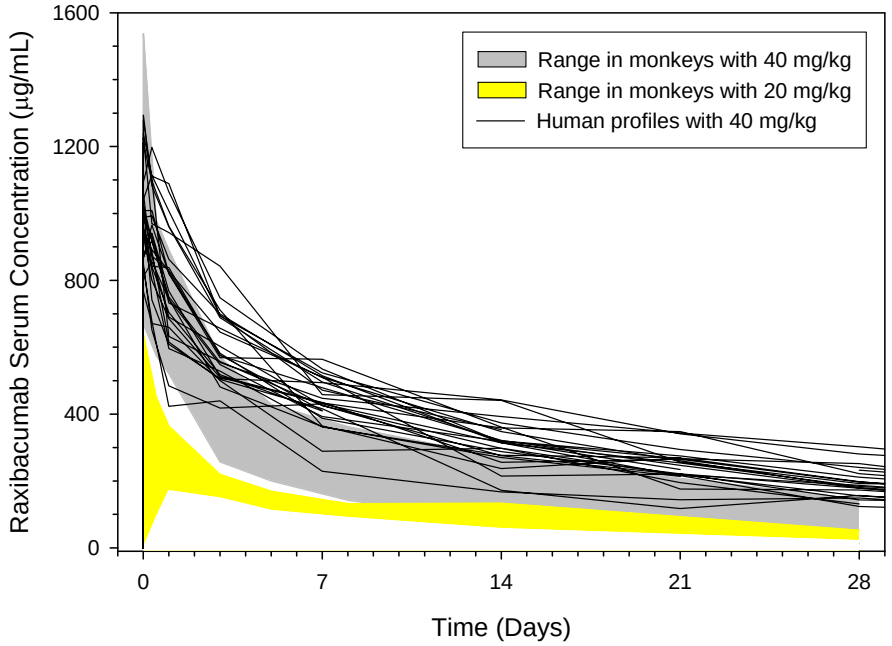
Figure 6.1-2. **Individual Serum Concentration-Time Profiles for Raxibacumab Following Single Intravenous Administration of 40 mg/kg in Healthy, Male and Female Subjects and 20 mg/kg and 40 mg/kg in Monkeys and Rabbits with Inhalation Anthrax**



Serum concentration profiles in red represent animals that died.

Figure 6.1-3. **Range of Serum Concentrations of Raxibacumab in Monkeys Following 20 mg/kg and 40 mg/kg Single IV Doses Versus Individual Serum Concentration-Time Profiles for Raxibacumab Following Single Intravenous Administration of 40 mg/kg in Humans**

Graph A: data to 28 days



Graph B: data to 7 days

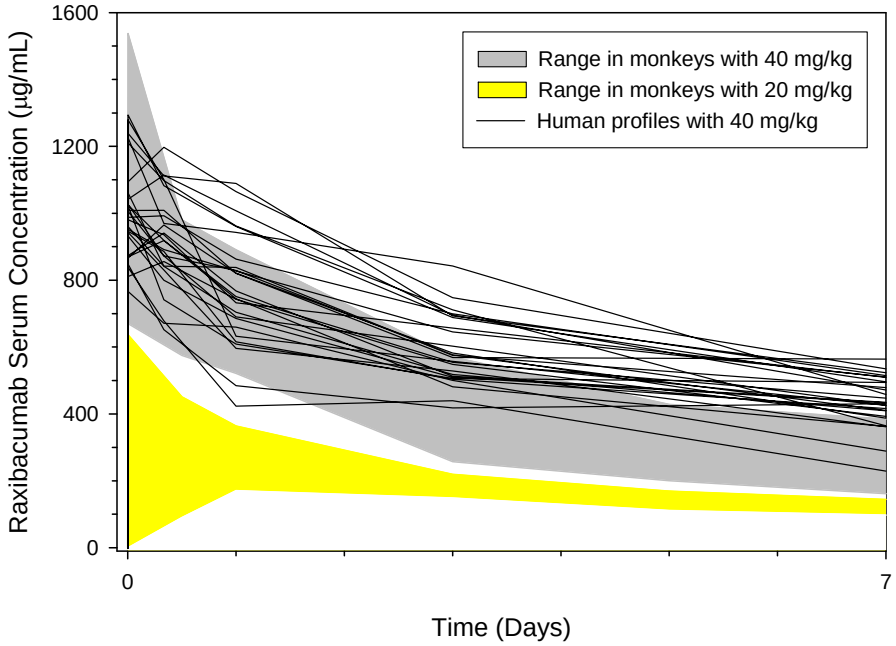


Figure 6.1-4. **Range of Serum Concentrations of Raxibacumab in Rabbits Following 20 mg/kg and 40 mg/kg Single IV Doses Versus Individual Serum Concentration-Time Profiles for Raxibacumab Following Single IV Administration of 40 mg/kg in Humans**

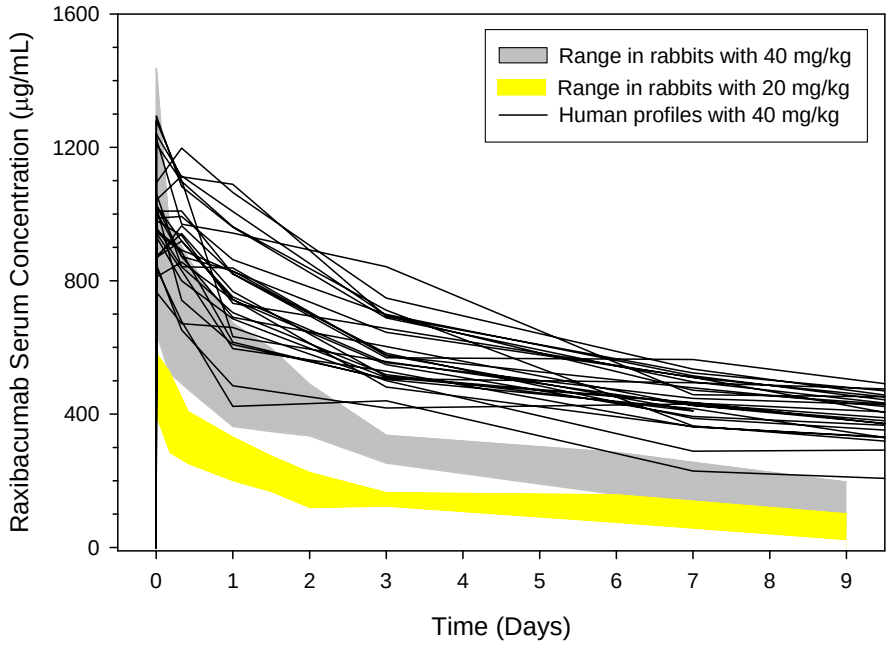
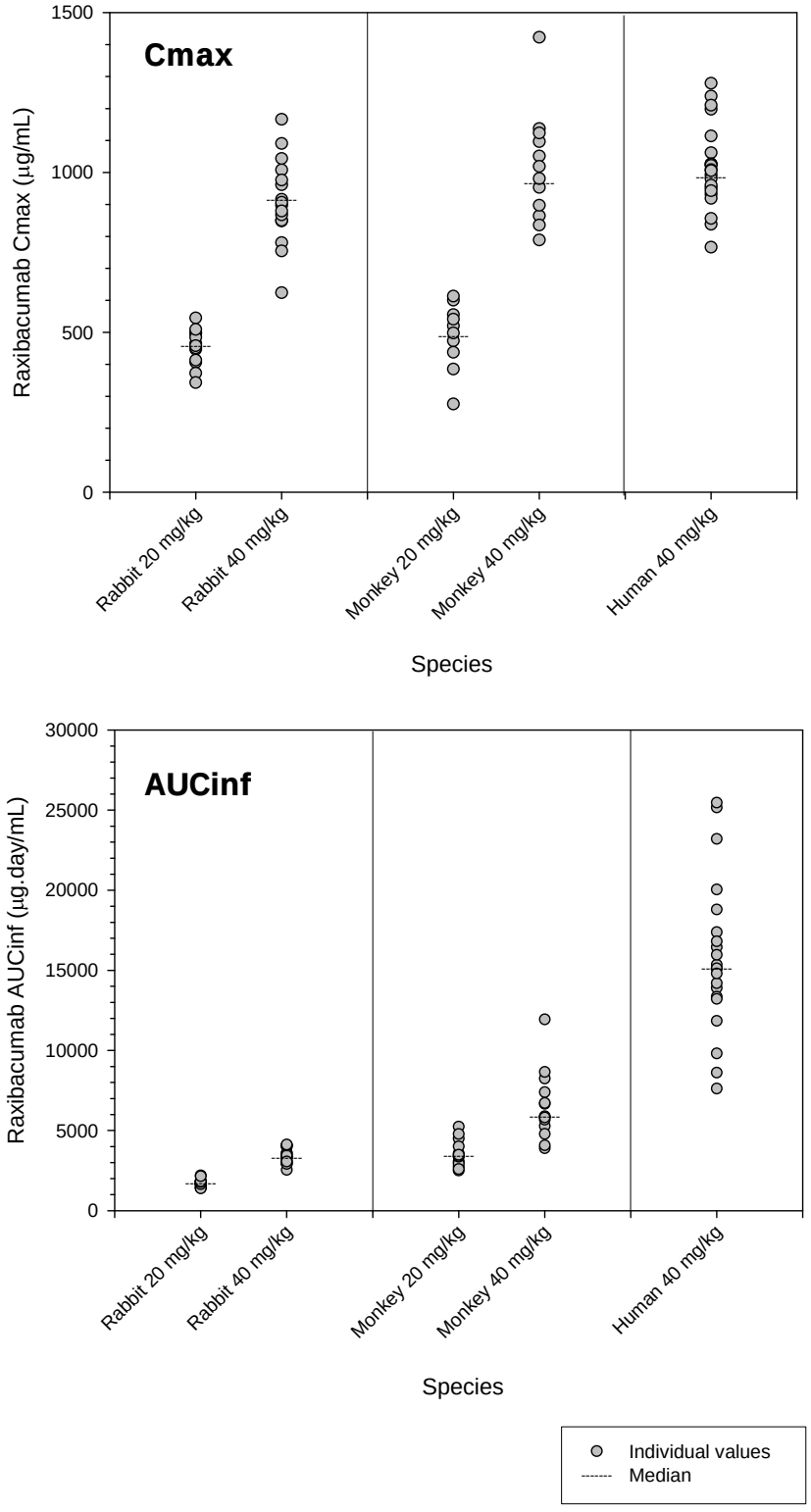


Figure 6.1-5. **Individual Raxibacumab Cmax and AUCinf Values Following Single Intravenous Administration of 40 mg/kg in Healthy, Male and Female Subjects and 20 mg/kg and 40 mg/kg in Monkeys and Rabbits with Inhalation Anthrax**



6.2 Drug Interactions

In the course of treatment of a *B. anthracis* infection and in response to an anthrax-related emergency, raxibacumab will likely be administered concurrently with an antimicrobial agent, such as a fluoroquinolone active against *B. anthracis*. To assess the influence of coadministration of the fluoroquinolone antimicrobial on raxibacumab exposure, a Phase 1 drug interaction study with raxibacumab and ciprofloxacin in healthy subjects (HGS1021-C1064) was conducted.

HGS1021-C1064 was an open-label study to evaluate the effect of raxibacumab on ciprofloxacin PK as well as the safety and PK of raxibacumab in combination with ciprofloxacin in healthy adult male and female subjects. Three treatment groups were evaluated. Group 1 received PO ciprofloxacin (500 mg Q12h, Days 0 to 7), with a single raxibacumab (40 mg/kg) dose IV on Day 5. Group 2 received a single raxibacumab (40 mg/kg) dose IV on Day 0. Group 3 received a single IV ciprofloxacin (400 mg) dose on Day 0 immediately followed by a single IV raxibacumab (40 mg/kg) dose, a second IV ciprofloxacin (400 mg) dose 12 hours later, and then PO ciprofloxacin (500 mg Q12h, Days 1 to 7) for a total of 13 doses.

Pharmacokinetic parameters for raxibacumab following single intravenous administration of 40mg/kg with and without coadministration of ciprofloxacin PO (Group 1) or IV/PO (Group 3) in healthy, male and female subjects are summarized in Table 6.2-1. Serum raxibacumab concentration-time profiles were very similar among treatment groups, with overlapping SD error bars. Statistically significant differences in PK parameters were not encountered for Group 3 (raxibacumab + IV ciprofloxacin) versus the raxibacumab alone group. Overall, exposure to ciprofloxacin appears to have no consistent or meaningful impact on raxibacumab PK.

Table 6.2-1 Summary of Raxibacumab Concentrations Following a Single 40 mg/kg Raxibacumab IV Infusion Administered with or without PO or IV Ciprofloxacin

Parameter	Group 1[a] (n = 27)	Group 2[b] (n = 27)	Group 3 (n = 28)
Cmax (µg/ml)	1143.3 ± 169.5 (833.6 – 1517.8)	1020.3 ± 140.6 (766.2 – 1293.7)	1047.8 ± 180.3 (772.5 – 1458.4)
AUCinf (µg·day/ml)	14871.9 ± 3821.1 (5494.5 – 21116.6)	15845.8 ± 4333.5 (7614.9 – 25464.6)	16349.3 ± 4255.7 (7117.5 – 27465.2)
Half life (days)	19.8 ± 8.18 (4.27 – 45.8)	20.6 ± 6.54 (5.93 – 32.3)	21.5 ± 8.92 (6.53 – 42.9)
CL (ml/day/kg)	2.99 ± 1.38 (1.85 – 7.30)	2.73 ± 0.84 (1.57 – 5.24)	2.63 ± 0.82 (1.46 – 5.62)
Vss (ml/kg)	64.9 ± 11.9 (44.1 – 99.8)	69.7 ± 13.7 (45.6 – 106.7)	67.2 ± 12.6 (47.6 – 93.2)

Group 1, raxibacumab 40 mg/kg + cipro PO
Group 2, raxibacumab 40 mg.kg only
Group 3, raxibacumab 40 mg/kg + cipro IV/PO
Data presented represents mean ± one standard deviation and (minimum – maximum)
[a] Subjects US003-000006 and US003-000028 excluded for receiving only partial doses of raxibacumab. Subject US003-00029 excluded for PK profile uncharacteristic of IV administration.
[b] Subject US003-000002 excluded for receiving only a partial dose of raxibacumab.

Pharmacokinetic parameters for ciprofloxacin following oral administration and IV followed by oral administration with and without coadministration of a raxibacumab 40 mg/kg single dose in healthy, male and female subjects are summarized in Table 6.2-2.

Table 6.2-2. Summary of Ciprofloxacin Pharmacokinetic Parameters Following Oral Administration (Group 1) or Intravenous Followed by Oral Administration (Group 3) with and without a Single Intravenous Dose of Raxibacumab 40 mg/kg in Healthy, Male and Female Subjects

Parameter	Group 1		Group 3	
	PO without Raxibacumab (n = 30)	PO with Raxibacumab (n = 30)	IV with Raxibacumab (n = 28)	PO with Raxibacumab (n = 28)
Cmax (ng/ml)	NA	NA	1854 (402)	NA
Css,max (ng/ml)	1436 (519)	1419 (599)	NA	1195 (566)
AUCinf (ng·hr/ml)	NA	NA	8770 (1877)	NA
AUCtau (ng·hr/ml)	7694 (2680)	8151[a] (2673)	NA	6615 (3224)
Half life (hr)	4.74 (2.09)	5.25[a] (2.47)	4.53 (0.89)	4.62[b] (1.07)
CL or CL/F (L/hr)	72.4 (24.0)	66.8[a] (21.9)	47.6 (9.8)	91.1 (36.9)
Vss (L)	NA	NA	285.9 (725.9)	NA
Vz or Vz/F (L)	510.7 (340.3)	486.0[a] (212.8)	312.0 (933.7)	630.7[b] (308.6)

Data presented as mean (SD).
Group 1, raxibacumab 40 mg/kg + cipro PO, Group 3, raxibacumab 40 mg/kg + cipro IV/PO
[a] n = 29
[b] n = 27
Source: HGS1021-C1064 Pharmacokinetic Report, Section 3.5.1.4

Upon statistical comparison for Css,max and AUCτ, the 90% CI fell within the 80% to 125% range, demonstrating that for those primary parameters Dose 11 (with raxibacumab) was equivalent to Dose 9 (prior to raxibacumab administration). In summary, there is no interaction between raxibacumab and ciprofloxacin; ciprofloxacin exposure is equivalent for ciprofloxacin administered alone and when administered with raxibacumab.

6.3 Exposure-Response for Efficacy

Exposure-response (E-R) analyses for raxibacumab efficacy were performed by the applicant and the FDA. The following is a discussion of the analyses performed by the FDA. Survival rates by raxibacumab dose in the pivotal animal efficacy studies are summarized in Figure 6.3-1. Survival rates in both studies exhibited a dose-response for 20 mg/kg and 40 mg/kg doses of raxibacumab IV. Mirroring the dose-response seen with 20 and 40 mg/kg doses of raxibacumab, a concentration-response is seen between the probability of survival and quantiles of raxibacumab Cmax, as presented in Figure 6.3-2. The data suggest a relationship between raxibacumab dose, concentration, and survival. Although it is proposed that a sufficiently high

Cmax optimizes the likelihood of efficacy, a threshold of Cmax could not be identified with the available data.

Figure 6.3-1 **Percent Survival in Rabbits and Monkeys Treated with Raxibacumab for Anthrax**

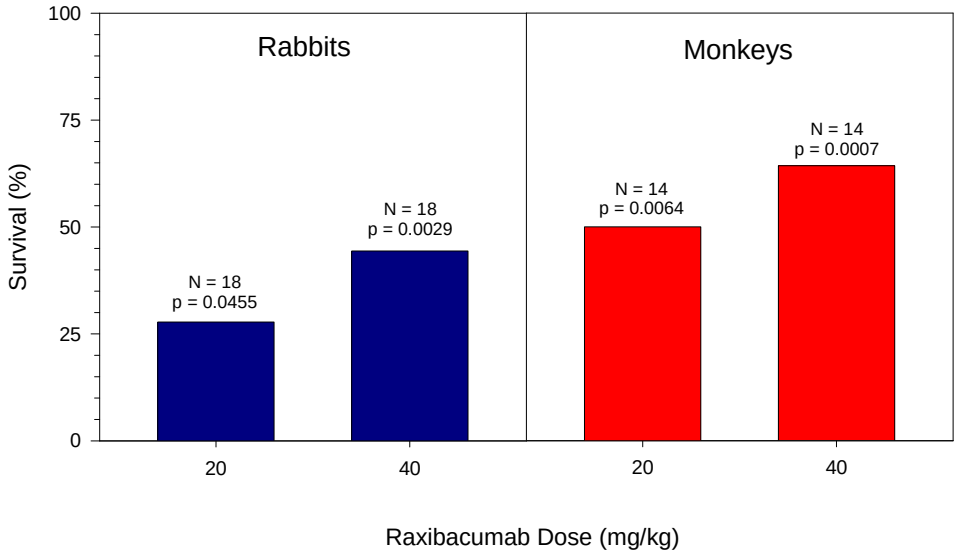
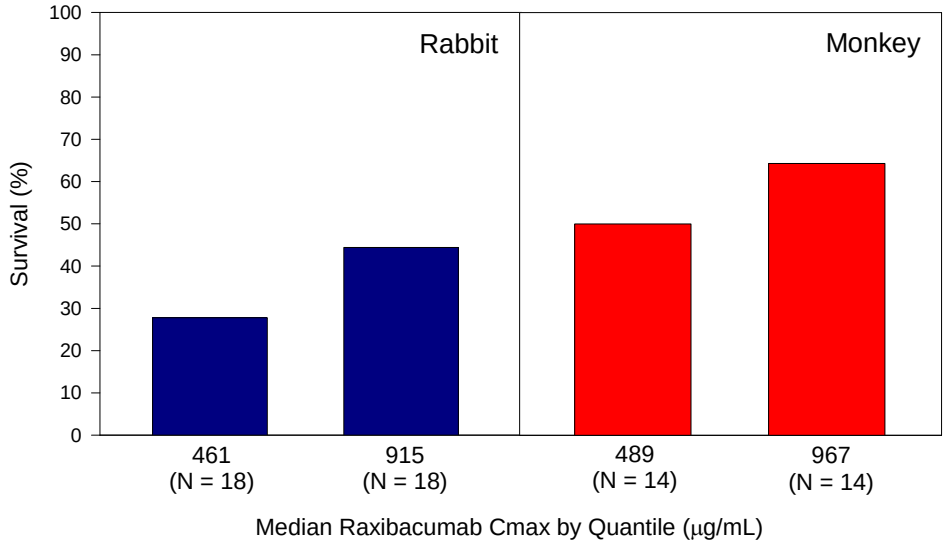


Figure 6.3-2 **Comparison of Probabilities of Survival by Raxibacumab Cmax Quantile**



The definition of an exposure-response relationship between raxibacumab and protective antigen (PA) concentrations is confounded by the following factors: 1) for both analytes, only total serum/plasma concentrations were measured, 2) the measurement of PA concentrations is affected by the presence of raxibacumab in serum and plasma, and 3) significant inherent intra- and inter-individual pharmacodynamic variability of PA data exists. A reasonable assessment of the inter-relationship between raxibacumab concentrations, PA concentrations and survival for

purposes of predicting the acceptability of a proposed dose is a comparison of raxibacumab serum concentrations over time to the concentrations required for 99.0 and 99.9% binding of PA (based on the known mechanism of action and binding kinetics of raxibacumab). Based on in vitro binding kinetics studies, serum raxibacumab concentrations of approximately 40 and 202 µg/mL are required for 99.0 and 99.9% binding of PA, respectively. As presented in Figure 6.3-3, in human subjects that received 40 mg/kg raxibacumab IV, raxibacumab concentrations remained above 202 µg/mL for 7 days and above 40 µg/mL for 42 days for all human subjects. Thus, in humans a 40 mg/kg dose of raxibacumab would be expected to maintain levels required for virtually complete binding of PA for 7 days.

Despite the theoretical importance of targeting virtually complete binding of PA, the duration of time raxibacumab concentrations remain above the threshold of 202 µg/mL does not appear to impact efficacy, as displayed in Figures 6.3-4 and 6.3-5. In both rabbits and monkeys, the amount of time serum concentrations of raxibacumab remained above 202 µg/mL generally did not differ between survivors and non-survivors.

Figure 6.3-3 **Individual Serum Concentrations of Raxibacumab in Human Subjects Following Administration of 40 mg/kg IV Compared to the Concentrations Required for 99 and 99.9% Binding of PA**

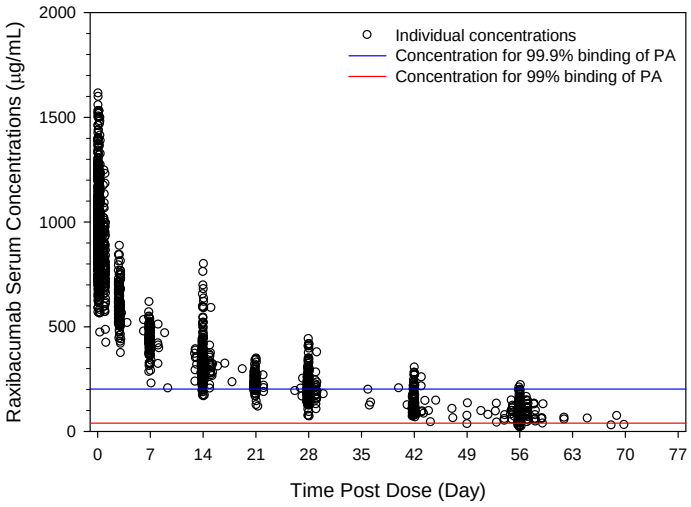


Figure 6.3-4 **Spaghetti Plot of Serum Concentration-Time Profiles for Raxibacumab Following Single Intravenous Administration of 20 mg/kg and 40 mg/kg Raxibacumab in Spore-Challenged Rabbits**

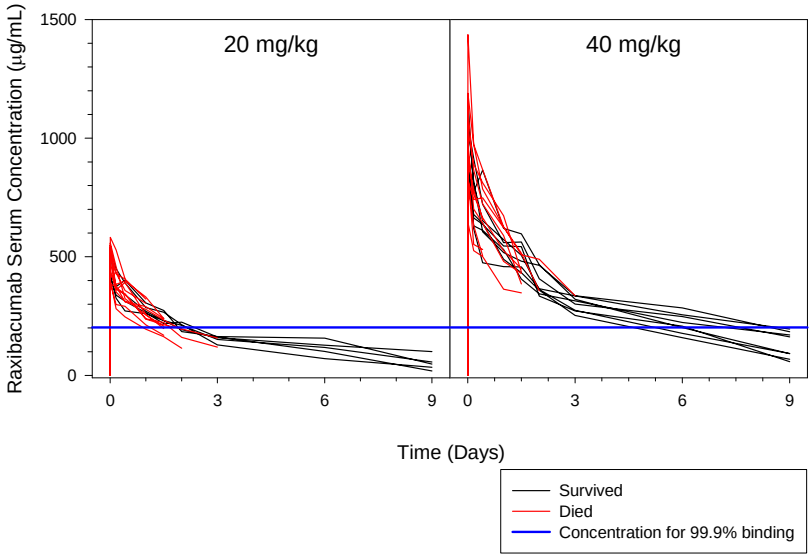
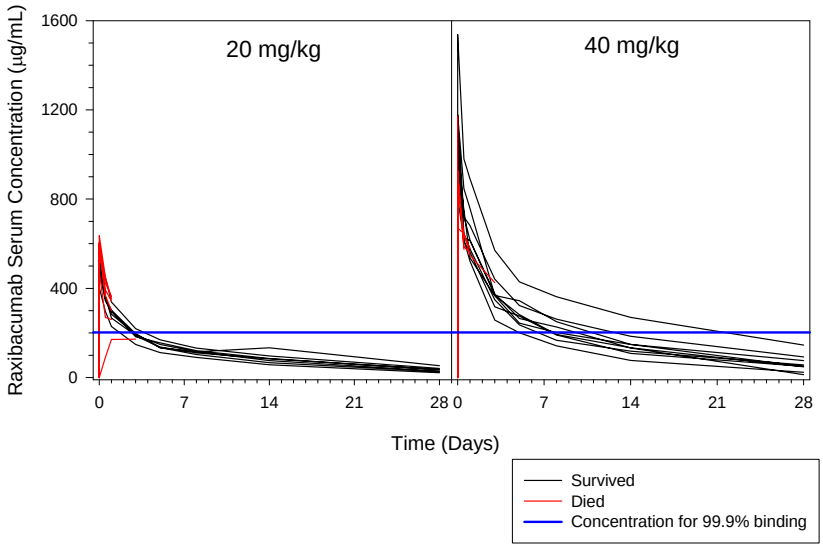


Figure 6.3-5 **Spaghetti Plot of Serum Concentration-Time Profiles for Raxibacumab Following Single Intravenous Administration of 20 mg/kg and 40 mg/kg Raxibacumab in Spore-Challenged Monkeys**



7 Safety

7.1 Nonclinical Pharmacology/Toxicology Safety

7.1.1 Tissue Cross-Reactivity of Raxibacumab

Two tissue cross-reactivity studies with HGS1021-Raxibacumab PA mAb showed an absence of positive staining in a majority of donor tissues from human, cynomolgus monkey, and New Zealand White rabbit at two different antibody concentrations. In particular, no tissue cross-reactivity was observed in the brain (cerebrum and cerebellum) or spinal cord of any species examined. However, cross-reactive binding with PA mAb was evident in the thyroid in both studies, showing strong, punctuate, staining of cytoplasmic granules in follicular epithelium. In Study 1494-95 (2003), positive staining of thyroid tissue was noted to be greater in monkeys than humans, whereas in study no. 1M1634 (2008), equally strong antibody binding in both human and monkey donor thyroid tissue was detected with complete absence of tissue reactivity in the rabbit. Weak, inconsistent staining of skeletal muscle (both humans and monkeys), endometrium (humans only), and breast and prostate (monkeys only) tissues was also reported in the earlier study which was not observed in the study completed in 2008. The cause(s) for the difference in results between the two studies is unknown but may have resulted from the different manufacturing process used to generate each antibody (developmental process versus the to-be-marketed product, M11). Alternatively, donor thyroid tissue from rabbit may contain specific or non-specific off-target binding sites different from monkeys and humans which prevented binding of human PA mAb in this species.

7.1.2 General Toxicity of Raxibacumab in Healthy Cynomolgus Monkeys

Healthy cynomolgus monkeys treated with raxibacumab (40 mg/kg) showed no significant evidence of toxicity in a 120-day repeat dose study (Study 6962-140). Raxibacumab was administered three times (once every 12 days) by either intravenous or subcutaneous injection (Phase 1) plus a single intramuscular injection (to both cohorts) on day 69 (Phase 2). All monkeys survived with no reported test article effects different from the control group.

Toxicokinetic analysis in healthy monkeys treated with raxibacumab in the 120 day study can be found in Table 7.1.2-1.

Table 7.1.2-1 Mean PA mAb concompartmental PK parameters in cynomolgus monkey following IV, SC, or IM doses at 40 mg/kg

Parameter		IV, 40 mg/kg	SC, 40 mg/kg
$AUC_{(0-\infty)}$	µg•day/mL	31608 ± 3628	25718 ± 6582
$t_{1/2}$	day	12.4 ± 1.6	14.0 ± 2.7
		Phase 1, Dose 1	
$C_{max,1}$	µg/mL	1088.8 ± 112.8	417.8 ± 121.5
		Phase 1, Dose 2	
$C_{max,2}$	µg/mL	1193.2 ± 175.3	647.1 ± 201.7
		Phase 1, Dose 3	
$C_{max,3}$	µg/mL	1357.6 ± 121.9	801.4 ± 194.2
		Phase 2, Dose 1	
$C_{max,4}$	µg/mL		477.3 ± 64.6

(Modification of table 2 located on page 14 of HGS study report AB50409.INF.0.034)

No obvious sex-dependent differences in raxibacumab were observed. Forty-eight hours after the first IV dose of raxibacumab in Phase 1, maximum blood levels were twice the level detected after the SC injection. Serum values increased 1-2 fold after the third IV or SC dose on Day 25, and $AUC_{(0-\infty)}$ exposure after IV administration was nearly 2-fold greater than levels observed following SC dosing. Despite the differences in Cmax and AUC, near equal terminal half-lives ($t_{1/2}$) of 12-14 days were observed with either route of administration and were similar to the mean ($t_{1/2}$) reported in cynomolgus monkey after a single dose. A single IM dose of PA mAb administered on day 69 resulted in serum concentrations similar to levels observed after the first SC dose. Dose normalized serum concentration at 40 mg/kg in this study was similar to 1 and 10 mg/kg for both the IV and SC routes in the single dose study, indicating dose linearity with no antibody neutralization across a 40-fold range.

No immunogenic response above background levels was detected in healthy cynomolgus monkeys treated with raxibacumab in the 120-day study. Antibodies against the Fab and Fc portion of the PA mAb antibody in raxibacumab-treated animals failed to increase above control levels determined from normal sera from 50 untreated monkeys. However, several deficiencies in the study report including the absence of critical individual baseline data preclude any findings and conclusions reported from this study.

7.1.3 Reproductive Toxicology of Raxibacumab in Healthy New Zealand White Rabbits

Healthy New Zealand White rabbits treated with raxibacumab (40 or 120 mg/kg) showed no evidence of test-article related maternal or embryo-fetal developmental toxicity different from controls (Study 6962-173). Raxibacumab was administered on gestation day (GD) 7 and again on GD 14 by intravenous injection. Maternal reproductive parameters including weight gain, pregnancy rates, number of pre-implantation loss and resorptions, numbers of corpora lutea, and implantation sites were comparable between treated and control animals. Sex ratios, fetal weight, external anatomy, and soft tissue malformations in offspring from raxibacumab treated pregnant dams were no different than in pups delivered from vehicle treated maternal controls. Two skeletal variations (unossified 5^{th} sternebra and presence of 13^{th} rudimentary ribs) were

present in the high dose group, the latter exceeding historical range, however these deviations were considered not to be a drug-related adverse effect.

Toxicokinetic analysis in raxibacumab-treated pregnant dams (n = 3 per dose) in the above mentioned study showed significantly higher mean serum raxibacumab concentrations at all timepoints in the 120 mg/kg dose group relative to the 40 mg/kg dose group on GD 7, 9, 14, and 29. Dose-normalized serum concentrations of raxibacumab were the same across doses and groups, showing dose linearity across a 3 fold dose range. A trend towards a slightly lower serum concentration of raxibacumab in several animals with detectable levels of anti-PA mAb antibodies was detected at both doses. In addition, several animals negative for the anti-raxibacumab antibodies in the 120 mg/kg dose group also showed decreased serum drug levels, suggesting neutralization of drug levels by circulating anti-raxibacumab antibodies and/or assay interference from serum raxibacumab concentrations in excess of 150 μg/mL, shown to decrease assay sensitivity for anti-raxibacumab antibodies. The raxibacumab concentration-time profiles presented in pregnant rabbits in this study were similar to those predicted from non-pregnant rabbits (HGS AB50409.INF.0.016). However, no derived PK values (e.g. C_{max}, AUC) were presented.

The overall incidence of anti-raxibacumab antibody response in pregnant New Zealand White dams above background levels was very low (5/138). However, findings of anti-raxibacumab antibodies in an untreated control animal combined with high serum levels of raxibacumab > 150 μg/mL in the 120 mg/kg dose group may have reduced the sensitivity of the assay for the anti-PA mAb response. Of 11 samples from the 120 mg/kg group that exceeded the raxibacumab serum limit, seven were negative, four were potentially positive, and only one confirmed positive in the assay. Such potentially confounding results may preclude any findings and conclusions reported from this study.

7.2 Clinical Safety

A total of 326 healthy volunteers received the recommended dose of raxibacumab of 40 mg/kg manufactured by the M11 process (the to-be-marketed product) and were evaluated for safety of raxibacumab. Of these, 303 subjects received a single dose (Study HGS1021-C1064 and Study HGS1021-C1063), 23 subjects received a second dose two weeks after their first dose (Study HGS1021-1063), and 20 subjects from Study HGS1021-C1064 received a 2nd dose more than 4 months after their initial dose (Study HGS1021-C1069). In Study HGS-1021-C1064, 48 subjects who received raxibacumab also received ciprofloxacin as part of this drug interaction study.

Studies HGS1021-C1064, HGS1021-C1063 and HGS1021-C1069 are briefly summarized in the Table 7.2-1 below.

Table 7.2-1: Studies in Healthy Volunteers included in the Safety Analysis

Study ID	Design Control Type	Group: Entered/ Completed	Indication	Sex M/F; Median age (range); Race	Duration	Study and Control Drug, Route, Regimen, Dosing frequency
HGS-1021-C1063	P3, R, SB, PC, RD	Double dose raxibacumab:24/23 Double dose placebo: 8/5 Single dose raxibacumab: 216/206 Single dose placebo: 72/68	Safety and PK in healthy subjects with single and repeat injection	156M/164F; 39.8 (18-88); 259W, 30B, 24A, 13NL, 10MR, 5NH	Single-dose (day 0) Double-dose (days 0 and 14) with 56 day follow-up	Raxibacumab, IV Placebo, IV; Single dose (day 0), double dose (days 0 and 14)
HGS-1021-C1069	P2/3, SG. OL, RD	All 20 subjects treated with a single 40 mg/kg IV raxibacumab dose at least 4 months after an initial 40 mg/kg. Single dose administered IV during study HGS-1021-C1064	Safety and PK in healthy subjects with repeat injection	12M/8F; 38.5 (22-61); 13W, 7B, 4HL	Single-dose with 56 day follow-up	Raxibacumab, IV; single dose
HGS-1021-C1064	P2/3, R, OL, single-dose	PO cipro, IV raxi : 32/26 IV raxi: 28/22 IV cipro, IV raxi :28/22	Safety and PK in healthy subjects with concomitant use with ciprofloxacin	43M/45F; 34.4 (18-61); 53W, 31B, 3NL, 1BNH, 21HL	7 days with 56 day follow-up	Raxibacumab IV; Ciprofloxacin PO; Ciprofloxacin IV Raxibacumab IV single dose; Cipro PO Q12h, 15 doses, Cipro IV 2 doses 12h apart

A, Asian; Al, American India; B, Black; BNH, Black and Native Hawaiian; HL Hispanic or Latino; MR, Multiracial; NH Native Hawaiian; NL Not listed; W, White
CPL, Cipro, Ciprofloxacin
OL, Open label; P1, Phase 1; P2/3, Phase 2/3; P3, Phase 3
P, Placebo; PC, Placebo-controlled; R, Randomized; RD Repeat dose; SB, Single blind; SG, Single Group; Tx, Number of subjects treated

Demographics for all 326 subjects are shown below in Table 7.2-2. Most subjects were white, within a median age of 38 years (range 18 to 88 years) with a similar number of males and females enrolled.

Table 7.2-2: Demographics of Subjects Enrolled Across Studies (from HGS' submission)

	Single-Dose (HGS1021-C1063 + HGS1021-C1064[1]) N = 283	Double-Dose ≥ 4 Months Apart (HGS1021-C1069) N = 20	Double-Dose 14 Days Apart (HGS1021-C1063) N = 23	All Raxibacumab Treated (HGS1021-C1064/ HGS1021-C1069[2] +HGS1021-C1063) N = 326
Sex				
Male	130 (45.9 %)	12 (60.0 %)	10 (43.5 %)	152 (46.6 %)
Female	153 (54.1 %)	8 (40.0 %)	13 (56.5 %)	174 (53.4 %)
Race[3]				
White	207 (73.1 %)	14 (70.0 %)	21 (91.3 %)	242 (74.2 %)
Asian	18 (6.4 %)	-	-	18 (5.5 %)
Black or African American	48 (17.0 %)	6 (30.0 %)	1 (4.3 %)	55 (16.9 %)
American Indian or Alaska Native	1 (0.4 %)	-	-	1 (0.3 %)
Native Hawaiian or Other Pacific Islander	5 (1.8 %)	-	-	5 (1.5 %)
Not Listed	14 (4.9 %)	-	1 (4.3 %)	15 (4.6 %)
Multiracial	9 (3.2 %)	-	-	9 (2.8 %)
Hispanic or Latino origin	46 (16.3 %)	3 (15.0 %)	1 (4.3 %)	50 (15.3 %)
Age (years)[4]				
n	283	20	23	326
Mean ± SD	39.0 ± 15.4	40.5 ± 13.3	48.5 ± 14.6	39.8 ± 15.3
Median	36.5	38.5	50.5	37.4
Range	(18.1, 87.9)	(22.4, 60.6)	(22.1, 76.2)	(18.1, 87.9)
Age group				
< 65 years	264 (93.3 %)	20 (100.0 %)	21 (91.3 %)	305 (93.6 %)
>= 65 years	19 (6.7 %)	-	2 (8.7 %)	21 (6.4 %)
Weight (kg)				
n	283	20	23	326
Mean ± SD	76.3 ± 17.3	78.4 ± 13.9	82.6 ± 19.2	76.9 ± 17.3
Median	74.7	77.2	79.9	75.6
Range	(44.6, 155.9)	(56.5, 98.6)	(54.8, 121.6)	(44.6, 155.9)

1 Excluded the 20 subjects who received a 2nd Raxibacumab dose in HGS1021-C1069.

2 Subjects participating in both HGS1021-C1064 and HGS1021-C1069 were counted once only with race, age, and weight based on HGS1021-C1064.

3 Subjects who checked more than one race category were counted under individual race categories as well as the multiracial category.

4 Age was calculated from the date of birth to the date of randomization.

Findings

Deaths

There was one death reported among the 326 subjects. Subject US001-002 was enrolled in study HGS1021-C1063 and randomized to the placebo double-dose group. This subject died from injuries sustained in a motor vehicle accident. A narrative of the event follows:

> Subject US001-002, was a 45-year-old white female in the placebo double-dose group, who received the infusions of study drug per protocol on Day 0 and Day 14. No relevant medical history or concomitant medications were reported. The subject was involved in a motorcycle accident that occurred 25 days after the 2nd placebo dose (Day 39), and died as a result of injuries sustained in the accident. The investigator indicated that the injuries sustained in the accident (life-threatening) were not related to study agent.

Serious Adverse Events (SAEs)[22]

Three subjects (0.9%) experienced an SAE which are shown in Table 7.2-3.

Table 7.2-3: SAEs reported across all studies

Study	Treatment received	Subject ID	A/S /R	MedDRA system organ class	Preferred Term	AE Start Day/ Duration (days)	Outcome	Relationship to study drug	Action taken with study drug
HGS1021-C1063	Placebo double dose	US001-002	45/ F/W	Injury, poisoning and procedural	Injury	39/1	Fatal	Not related	None
HGS1021-C1063	Raxibacumab double dose	US002-017	52/ F/W	Hepatobiliary disorders	Cholecystitis	24/3	Recovered/ resolved	Possibly related	None
HGS1021-C1064	Raxibacumab single dose	US001-005	48/ B/ M	Psychiatric disorders	Schizophrenia	5/ ongoing	Not recovered/ not resolved	Probably not related	None

A/S/R: age/sex/race

There was one death in Study HGS1021-C1063 described previously. For both cases of cholecystitis and schizophrenia, these were unlikely to be due to raxibacumab based on temporal presentation (long duration between raxibacumab dosing and onset of the AE) and the presence of pre-existing conditions which could account for the SAE.

Dropouts and Discontinuations

There were no subject withdrawals due to adverse events (AEs). However, there were four subjects (1.2%) who experienced AEs and discontinued treatment, as shown in Table 7.2-4.

[22] Serious adverse events are defined as events that are life-threatening, resulted in hospitalization, death, permanent disability; a congenital malformation.

Table 7.2-4: Subjects with AEs Resulting in Discontinuation of Treatment

Study	Treatment received	Subject ID	A/S /R	Preferred Term	Serious/ Severity	Study Day	Relationship to study drug	Notes
HGS1021-C1064	Cipro/ raxibacumab	US003-006	36/ F/W	Urticaria	No/mild	5	Probably related	No premedication with diphenhydramine
HGS1021-C1064	Cipro/ raxibacumab	US003-028	56/ F/W	Clonus	No/mild	5	Probably related	"Left arm and leg clonic muscular contractions" and "facial flushing", both mild and resolved in 1 day; no change in vital signs
HGS1021-C1064	Raxibacumab single dose	US003-002	33/ F/W	Urticaria	No/mild	1	Probably related	No premedication with diphenhydramine
HGS1021-C1063	Raxibacumab single dose	US002-011	26/ M/ B	Dyspnea	No/mode rate	0	Probably not related	"Difficulty breathing" of moderate severity during infusion; no sx anaphylaxis or rash, no changes in vital signs; investigator attributed the subject's symptoms as most likely due to esophageal spasm caused by rapid eating prior to the infusion and/or anxiousness
HGS1021-C1063	Placebo double dose	US001-022	59/ M/ W	Skin infection	No/mode rate	12	-	

A/S/R: age/sex/race

Adverse Events of Severe Intensity

Adverse events (AEs) of severe intensity were reported in 1.9% of raxibacumab-treated subjects and are shown in Table 7.2-5.

Table 7.2-5: Severe AEs across Studies

MedDRA system organ class	MedDRA Preferred Term	Single Dose - C1063+C1064 N=283 (%)	Double Dose - C1063 N=23 (%)	All raxibacumab subjects* N=326 (%)
Hepatobiliary disorders	Cholecystitis	0	1 (4.4)	1 (0.2)
Infections and infestations	Influenza	1 (0.4)	0	1 (0.2)
Investigations	Blood amylase increased	1 (0.4)	0	1 (0.2)
	Blood creatine phosphokinase increased	1 (0.4)	0	1 (0.2)
	Prothrombin time prolonged	1 (0.4)	0	1 (0.2)
Psychiatric disorders	Schizophrenia	1(0.4)	0	1 (0.2)

*There were no AEs of severe intensity reported in the double dose separated by ≥ 4 months group (Study HGS1021-1069) although they are included in the Total Subject count

There were 2 severe and serious AEs in raxibacumab treated subjects (cholecystitis, schizophrenia) which were described previously. In placebo-treated subjects, there was a single event of severe leukocytosis reported. All other severe AEs were unlikely to be related to raxibacumab.

CNS

Based on the increased CNS findings in animals treated with raxibacumab but died of anthrax in the pivotal efficacy studies, CNS AEs were examined more closely in the human safety database.

In the SOC "Nervous system disorders", the following AEs were reported (Table 7.2-6).

Table 7.2-6: Nervous System Disorders across all Studies

MedDRA system organ class	MedDRA Preferred Term	Placebo* – C1063 N=80 (%)	Single Dose - C1063+C1064 N=283 (%)	Double Dose - C1063 N=23 (%)	Double Dose - C1069 N=20 (%)	All raxibacumab subjects N=326 (%)
Nervous system disorders	Clonus	0	1 (0.4)	0	0	1 (0.2)
	Dizziness	1 (1.3)	3 (1.1)	0	0	3 (0.6)
	Headache	8 (10)	25 (8.8)	1 (4.3)	5 (25)	31 (9.5)
	Lethargy	1 (1.3)	0	0	1 (5)	1 (0.2)
	Paraesthesia	0	1 (0.4)	0	0	1 (0.2)
	Somnolence	0	4 (1.4)	1 (4.3)	0	5 (1.5)
	Syncope vasovagal	0	2 (0.7)	0	0	2 (0.4)
	Tension headache	2 (2.5)	0	0	0	0

* includes both single (n=74) and double (n=6) dose placebo subjects

In the animal studies, the main CNS finding was meningitis, with the pathologic findings of inflammation, hemorrhage and necrosis. There were no CNS infections reported in the SOC "Infections and infestations" across all studies. Symptoms suggestive of meningitis are headache, fever and meningismus. Headache is nonspecific and was reported in similar numbers of placebo and raxibacumab treated subjects (10% and 9.5%, respectively). There were an additional two reports of tension headache in the placebo group.

With respect to subjects reporting any combination of the triad of symptoms suggestive of meningitis, there were no reports of meningismus across studies. There was one raxibacumab treated subject (US004-000030) enrolled in study HGS1021-C1063 who reported fever (mild) on day 41 in conjunction with vomiting (mild), both of one day duration with no action taken. Similarly, there was one placebo subject US005-000046 enrolled in Study HGS1021-C1063 with pyrexia and headache reported on Study day 36, again of one day's duration with no intervention. It is unlikely that either of these represented cases of meningitis.

Common Adverse Events
Adverse events according to System Organ Class (SOC) are shown in Table 7.2-7.

Table 7.2-7: AEs by System Organ Class

MedDRA system organ class	Placebo* N=80 (%)	Single Dose C1063+ C1064 N=283 (%)	Double Dose C1063 N=23 (%)	Double Dose C1069 N=20 (%)	Total double dose N=43 (%)	All raxibacumab subjects N=326 (%)
Blood and lymphatic system disorders	3 (3.8)	8 (2.8)	0	0	0	8 (2.5)
Cardiac disorders	1 (1.3)	2 (0.7)	0	0	0	2 (0.6)
Ear and labyrinth disorders	1 (1.3)	3 (1.1)	1 (4.4)	0	1 (2.3)	4 (1.2)
Eye disorders	0	3 (1.1)	0	0	0	3 (0.9)
Gastrointestinal disorders	9 (11.3)	26 (9.2)	2 (8.7)	2 (10.0)	4 (9.3)	30 (9.2)
General disorders and administration site conditions	3 (3.8)	22 (7.8)	0	2 (10.0)	2 (4.7)	24 (7.4)
Hepatobiliary disorders	0	0	1 (4.4)	0	1 (2.3)	1 (0.3)
Infections and infestations	15 (18.8)	30 (10.6)	5 (21.7)	2 (10.0)	7 (16.3)	37 (11.3)
Injury, poisoning and procedural complications	7 (8.8)	12 (4.2)	3 (13.0)	2 (10.0)	5 (11.6)	17 (5.2)
Investigations	1 (1.3)	12 (4.2)	1 (4.4)	0	1 (2.3)	13 (4.0)
Metabolism and nutrition disorders	1 (1.3)	1 (0.4)	1 (4.4)	0	1 (2.3)	2 (0.6)
Musculoskeletal and connective tissue disorders	6 (7.5)	20 (7.1)	2 (8.7)	1 (5.0)	3 (7.0)	23 (7.1)
Nervous system disorders	11 (13.8)	35 (12.4)	2 (8.7)	6 (30.0)	8 (18.6)	43 (13.2)
Psychiatric disorders	0	4 (1.4)	0	0	0	4 (1.2)
Reproductive system and breast disorders	1 (1.3)	3 (1.1)	0	0	0	3 (0.9)
Respiratory, thoracic and mediastinal disorders	5 (6.3)	15 (5.3)	0	0	0	15 (4.6)
Skin and subcutaneous tissue disorders	4 (5.0)	29 (10.3)	0	1 (5.0)	1 (2.3)	30 (9.2)
Social circumstances	0	1 (0.4)	0	0	0	1 (0.3)
Vascular disorders	2 (2.5)	5 (1.8)	0	0	0	5(1.5)

* includes both single (n=74) and double (n=6) dose placebo subjects

The most frequently reported SOCs in the raxibacumab treated subjects were Nervous system disorders (13.2%), Infections and infestations (11.3%), and Gastrointestinal disorders and Skin and subcutaneous tissue disorders (both 9.2%). These were all higher in the raxibacumab treated subjects compared to placebo.

CNS Adverse Events
In the Nervous System Disorders SOC, headache was by far the most frequently reported AE and was responsible for the difference in rates observed between the placebo and raxibacumab treated subjects. Headache was reported in 8.8% of single dose subjects, 14% of double dose subjects, and 10%

Infections/Infestations
In contrast, within the Infections and infestations SOC, upper respiratory tract infection occurred in 11.6% of double dose raxibacumab subjects, compared to 3.9% of single dose raxibacumab subjects and 5.0% of placebo subjects. However, other infections were not reported more frequently in the active treatment groups to suggest a uniform immune effect of raxibacumab. All AEs in the raxibacumab treated subjects ranged in frequency from 0.2% to 4.9%.

Gastrointestinal Events
In the Gastrointestinal disorders SOC, rates of abdominal pain, diarrhea, nausea and vomiting were all higher in the placebo group compared to all raxibacumab subjects.

Dermatologic (Skin and subcutaneous tissue) Events
Lastly, in the Skin and subcutaneous tissue disorders SOC, AEs reported by the raxibacumab treated subjects ranged from 0.2% to 1.8% in frequency. Pruritis and rash were reported in all raxibacumab subjects at 2.1% and 1.8% respectively, and were comparable to placebo rates (pruritis 0%, rash 1.3%). In Study HGS1021-C1064 evaluating raxibacumab PK in combination with ciprofloxacin, five of the first 25 subjects dosed with raxibacumab developed dermatologic events following administration. Three subjects responded to oral diphenhydramine, and two discontinued the infusion with resolution (one with diphenhydramine and one spontaneous). As a result of these findings, the protocol was amended so that all subsequent subjects received diphenhydramine before raxibacumab infusion. At the completion of HGS1021-C1064 a total of 8/88 (9.1%) subjects reported rash. In comparison, in a subset of subjects who did not receive diphenhydramine premedication rash occurred in 6/27 (22%) subjects. Furthermore, to closely match the anticipated use of raxibacumab in human inhalational anthrax, diphenhydramine pretreatment was also given to the monkeys participating in the inhalational anthrax efficacy studies.

Laboratory Findings
Laboratory tests with toxicity grade greater than or equal to 3 (severe) were infrequently reported. Table 7.2-8 summarizes these results.

Table 7.2-8: Laboratory Tests with Toxicity Grade Greater than or Equal to 3 (severe)

Lab Test code	Single Dose - C1063+C1064 N=283 (%)	Double Dose - C1063 N=23 (%)	Double Dose - C1064 N=20 (%)	All raxibacumab subjects N=326 (%)
ALT	1 (0.4)	0	0	1 (0.4)
AMYL	1 (0.4)	0	0	1 (0.4)
POTA	1 (0.4)	1 (4.4)	0	2 (0.4)
PT	2 (0.7)	0	1 (5.0)	3 (0.6)
WBC	2 (0.7)	0	0	2 (0.6)

Overall, the incidence of laboratory abnormalities was comparable between raxibacumab-treated and placebo-treated subjects (only active treatment AEs reported here). The incidence was not higher after a second raxibacumab administration than after a single administration. Most lab abnormalities were of low grade (Grade 2 or less), with grade 3 and 4 laboratory abnormalities infrequently reported, isolated and transient.

Special Populations
AEs were analyzed by sex, race and age, and no significant differences were found with these subgroup analyses.

7.3 Immunogenicity

Nonclinical:
No immunologic response above background levels was detected in healthy Cynomolgus monkeys treated with raxibacumab in the 120-day study. Antibodies against the Fab and Fc portion of the PA mAb antibody in raxibacumab-treated animals failed to increase above control levels determined from normal sera from 50 untreated monkeys.

The overall incidence of anti-raxibacumab antibody response in pregnant NZW dams above background levels was very low (5/138). However, we continue to have concerns about the reliability of these results due to questions about the immunogenicity assays. For more detailed information on the above studies please refer to the Sections 7.1.2 and 7.1.3 of this document.

Pivotal Animal Studies:
No immunogenicity assessments were performed in pivotal animal (both rabbits and NHP) efficacy studies

Combination Animal Studies:
Anti-raxibacumab immunogenicity assessments were added to Study 781-G923701 (NZW rabbits) as a protocol amendment to allow for determination of the impact of any observed anti-raxibacumab immunogenicity on plasma raxibacumab levels and survival.

Fifteen of 18 rabbits (83%) in the levofloxacin/raxibacumab group tested positive for anti-raxibacumab antibodies on Day 28. In addition, 6/19 (31.6%) rabbits in the levofloxacin group also tested positive for anti-raxibacumab antibodies on Day 28. HGS accounted for this finding by noting that although the levofloxacin only treatment group did not receive raxibacumab, the levofloxacin-treated rabbits mounted an anti-PA response which may have included antibodies that cross-reacted in the anti-human anti-PA assay. Given the modest incidence of anti raxibacumab immunogenicity at low titers compared with the raxibacumab-treated animals, this was felt to be a possible explanation. Furthermore, HGS pointed out that the emergence of potential anti-raxibacumab immunogenicity did not negatively impact survival.

Human
All four human safety studies looked for the development of an anti-raxibacumab antibody response, including PAM-NH-01 which used the developmental M10 formulation of the product. Table 7.3-1 summarizes the time points for immunogenicity assessments in Studies HGS1021-C1064, HGS1021-C1063 (second raxibacumab dose 2 weeks following first dose) and HGS1021-C1069 (second dose ≥ 4 months following first doseIn all studies, there were no

subjects who had a positive anti-raxibacumab antibody response following single or repeat (every 14 days or following ≥ 4 months) doses of raxibacumab.

Table 7.3-1 Immunogenicity Sampling in Raxibacumab Clinical Trials

Study	*Sampling Schedule for Anti-Raxibacumab Antibodies*
PAM-NH-01	Day 0 predose, and Days 14, 28, and 56/exit
HGS1021-C1063*	• Double-dose groups (Group 1 and Group 3): blood samples were collected prior to dosing on Day 0 and Day 14, and on Days 42 and 70/End of Study. • Single-dose groups (Group 2 and Group 4): blood samples were collected prior to dosing on Day 0, and on Days 28 and 56/End of Study.
HGS1021-C1064*	• Group 1: Blood samples were collected on Days 0 (prior to raxibacumab dose), 33, and 61/End of Study. • Group 2 and Group 3: Blood samples were collected on Days 0 (prior to prior to raxibacumab dose), 28, and 56/End of Study.
HGS1021-C1069*	Screening, prior to raxibacumab dosing on Day 0, and on Days 28, 56, and 70 (End of Study)

*Subjects found to have a positive anti-raxibacumab antibody titer following raxibacumab administration were to have serum collected approximately 6 months after the dose for follow-up immunogenicity assessment.

Immunogenicity testing comprised two assays (screening and confirmatory, please see details in the Appendix). The screening assay (direct binding) was an electrochemiluminescence (ECL)-based bridging assay, with rabbit polyclonal antibody used as a positive control. Samples identified as positive in the screening assay were to be confirmed positive in a confirmatory assay. The inhibition of binding confirmatory assay was performed identically to the direct binding screening assay with the exception that the samples were tested in parallel with excess unlabeled raxibacumab.

7.4 CNS Findings

7.4.1 Histopathology

In the pivotal efficacy Studies 682-G005758 (NZW rabbit) and 724-G005829 (Cynomolgus monkeys), an unexpected finding was that raxibacumab-treated animals that died had more CNS pathology consisting of hemorrhage, necrosis, inflammation and bacteria compared to placebo animals that died. Gross findings in the brains of monkeys that died were seen in 3/12 placebo, 6/7 in the 20 mg/kg group, 3/5 in the 40 mg/kg group. Number of animals with inflammation and CNS pathology from studies 724-G005829 and 682-G005758 are reported in Tables 7.4.1-1 and 7.4.1-2.

Table 7.4.1-1: Comparison of CNS Findings in Necropsized Animals by Treatment Group in Study 724-G005829 (Cynomolgus monkeys)

Treatment	Number of Necropsized Monkeys	No. (%) of CNS findings	P-value*
Moderate/Marked Brain Inflammation			
Placebo	n = 12	1 (8.3%)	
20 mg/kg Raxibacumab	n = 7	6 (85.7%)	0.0017
40 mg/kg Raxibacumab	n = 5	2 (40.0%)	0.1912
FDA CNS Pathology Level**			
Placebo	n = 12	1 (8.3%)	
20 mg/kg Raxibacumab	n = 7	6 (85.7%)	0.0017
40 mg/kg Raxibacumab	n = 5	3 (60.0%)	0.0525

* P values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.
** The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

Table 7.4.1-2: Comparison of CNS Findings in Necropsized Animals by Treatment Group in Study 628-G005758 (NZW rabbits)

Treatment	Number of Necropsized Rabbits	No. (%) of CNS findings	P-value*
Moderate/Marked Brain Inflammation			
Placebo	n = 16	0 (0%)	
20 mg/kg Raxibacumab	n = 12	3 (25.0%)	0.0672
40 mg/kg Raxibacumab	n = 11	3 (27.3%)	0.0564
FDA CNS Pathology Level**			
Placebo	n = 16	2 (12.5%)	
20 mg/kg Raxibacumab	n = 12	9 (75.0%)	0.0015
40 mg/kg Raxibacumab	n = 11	6 (54.5%)	0.0332

* P values are based on two-sided Fisher's exact test for comparisons between the raxibacumab group and placebo.
** The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

The hypothesis stated by HGS that this difference was related to longer survival of the raxibacumab-treated animals rabbits compared to the placebo group was carefully examined. Based on FDA's analysis, this finding does not seem plausible. The time of death was similar across the placebo and raxibacumab animals that died for both the monkey and the rabbit studies. However, within the raxibacumab groups, it appears the animals with CNS findings live longer than those without CNS findings.

Among the 12 placebo monkeys that died (Table 7.4.1-3), 11/12 had no brain inflammation, low pathology level, time from challenge to bacteremia of 1.32-5.34 days, time from treatment to death of 0.18-8.4 days, and a time from challenge to death of 1.92-10.75 days. The single monkey that had moderate brain inflammation and a high grade of pathology, the time from challenge to bacteremia was 1.48 days (no different from low pathology animals), time from treatment to death of 2.99 days (slightly longer than low pathology animals), and a time from challenge to death of 4.47 days (slightly longer than low pathology animals).

Table 7.4.1-3: FDA Pathologic Findings and various Time Measures in the Placebo Animals that died in Study 724-G005829 (Cynomolgus monkeys)

#	N=normal m=moderate M=marked Brain Inflammation	L=Low H=High Pathology Level*	Time from challenge to bact. (days)	Time from bact. to treat (days)	Time from treatment to death (days)	Time from challenge to death (days)
C23601	N	L	1.32	0.43	0.18	1.92
C23630	N	L	1.73	0.15	0.75	2.63
C23036	N	L	1.16	0.003	1.69	2.85
C23404	N	L	1.40	0.003	1.55	2.96
C24793	N	L	1.46	0.17	1.56	3.20
C24851	N	L	2.09	0.16	1.10	3.35
C24858	N	L	1.31	0.18	2.10	3.59
C24853	N	L	1.08	0.18	2.59	3.85
C24056	m	H	1.48	0.002	2.99	4.47
C24784	N	L	1.48	0.18	7.46	9.12
C23052	N	L	5.34	-3.00	8.40	10.75
C24824	N	L	1.94	-0.50	1.80	3.25

* The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

Of the seven monkeys in the raxibacumab 20 mg/kg IV group that died, 6/7 had moderate brain inflammation and a high pathology level, with time from challenge to bacteremia of 1.28-1.97 days, time from treatment to death of 1.54-3.36 days, and a time from challenge to death of 3.16-5.47 days (Table 7.4.1-4). The single monkey that died with no brain inflammation had a shorter time from challenge to bacteremia of 1.30 days, time from treatment to death of 0.82 days, and a time from challenge to death of 2.31 days, which could support the hypothesis that raxibacumab animals with more severe CNS findings lived longer in order to develop the more severe pathology.

Table 7.4.1-4: FDA Pathologic findings, and various time measures in the Raxibacumab 20 mg/kg animals that died in Study 724-G005829

#	N=normal m=moderate M=marked Brain Inflammation	L=Low H=High Pathology Level*	Time from challenge to bact. (days)	Time from bact. to treat (days)	Time from treatment to death (days)	Time from challenge to death (days)
C24856	N	L	1.30	0.19	0.82	2.31
C24755	**m**	**H**	**1.44**	**0.19**	**1.54**	**3.16**
C24066	**m**	**H**	**1.33**	**0.15**	**2.09**	**3.57**
C24878	**m**	**H**	**1.52**	**0.16**	**2.23**	**3.91**
C24840	**m**	**H**	**1.28**	**0.20**	**2.62**	**4.10**
C20255	**m**	**H**	**1.54**	**0.39**	**2.52**	**4.46**
C21466	**m**	**H**	**1.97**	**0.14**	**3.36**	**5.47**

* The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

Lastly, of the five monkeys in the raxibacumab 40 mg/kg IV group that died, 3/5 had a high pathology level (Table 7.4.1-5). The time intervals were as follows: time from challenge to bacteremia 1.47-2.02 days, time from treatment to death 2.04-3.64 days, and time from challenge to death 3.70-5.16 days. The 2 monkeys that died with no brain inflammation and low pathology did not have shorter times from challenge to bacteremia (1.30-1.49 days), although they did have shorter times from treatment to death 0.35-1.01 days, and shorter time from challenge to death 2.26-2.73 days.

Table 7.4.1-5: FDA Pathologic Findings, and various Time Measures in the Raxibacumab 40 mg/kg animals that died in Study 724-G005829

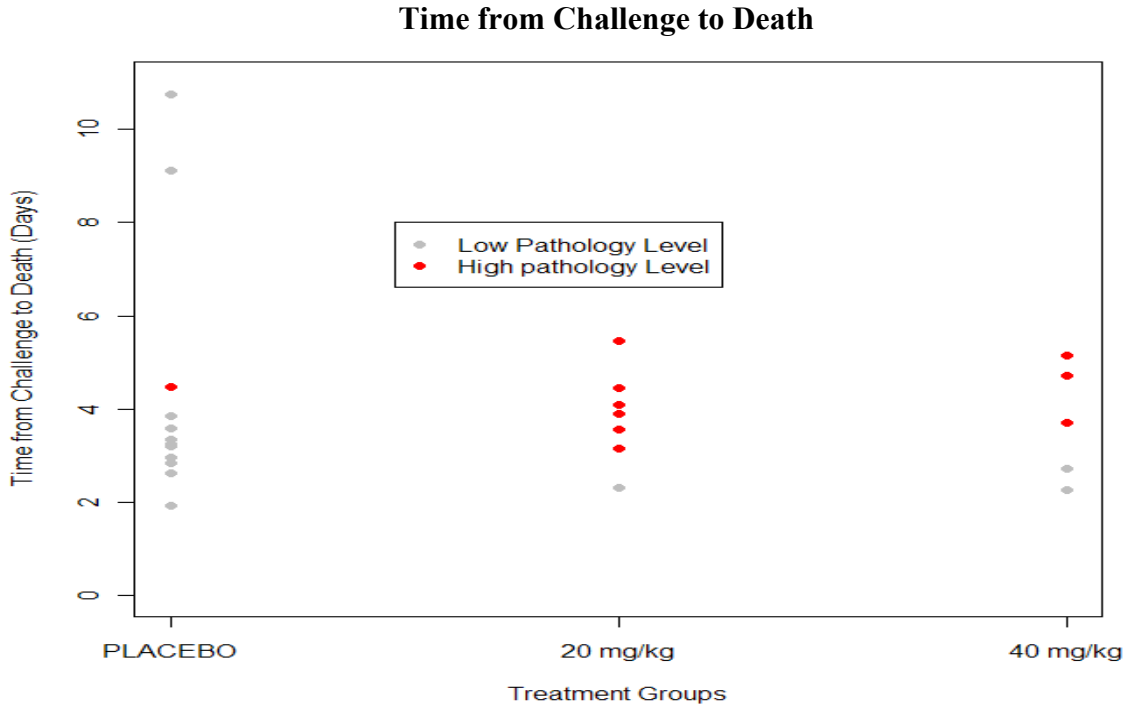
#	N=normal m=moderate M=marked Brain Inflammation	L=Low H=High Pathology Level*	Time from challenge to bact. (days)	Time from bact. to treat (days)	Time from treatment to death (days)	Time from challenge to death (days)
C23640	N	L	1.49	0.41	0.35	2.26
C24847	N	L	1.30	0.42	1.01	2.73
C23655	N	H	1.47	1.90	2.04	3.70
C24928	M	H	1.50	0.41	2.79	4.71
C23994	m	H	2.02	-0.501	3.64	5.16

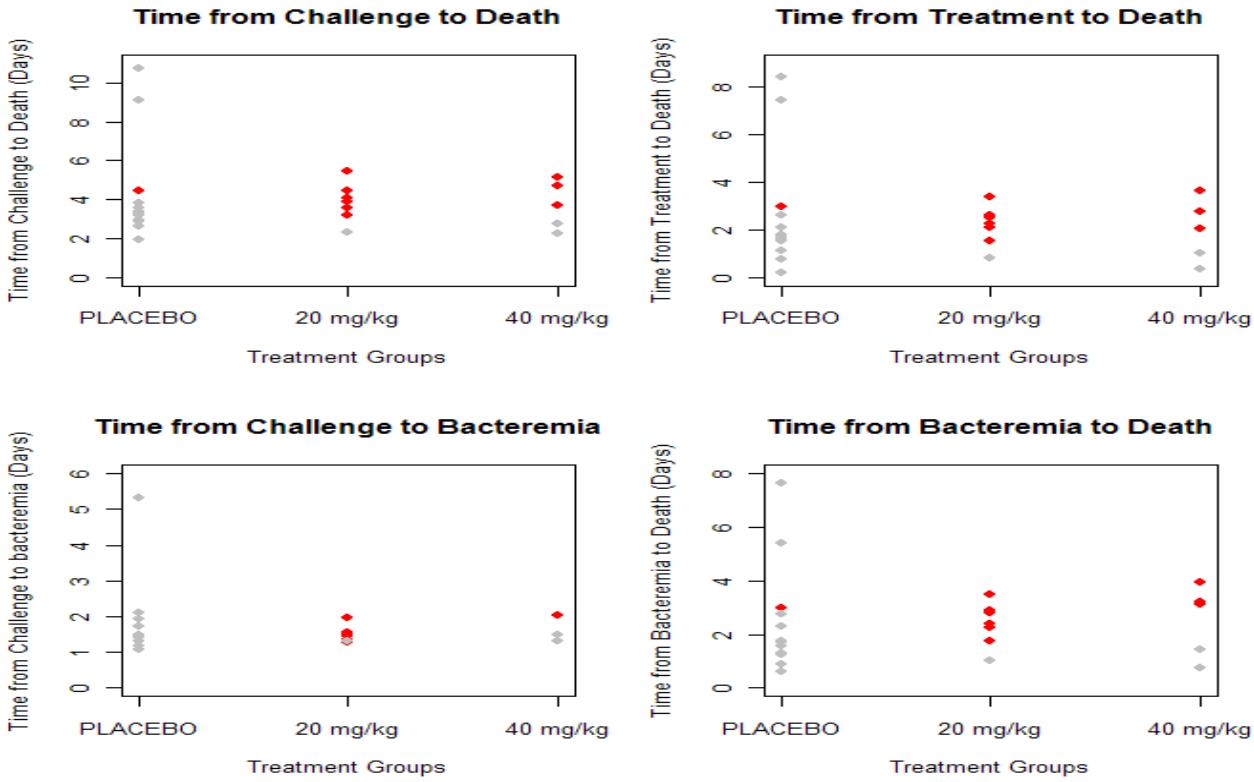
* The pathology level of CNS pathology findings was defined based on the following criteria: 1) For bacteria, inflammation and hemorrhage, the highest grade recorded was selected, 2) disregard grading of congestion as this represents intravascular hyperemia rather than a true pathologic findings, 3) grades 0-2 constitutes low level of pathology while 3-4 are considered high level, and 4) if necrosis is present, then elevate the pathology level to high if it was initially recorded as low.

Within their respective groups, raxibacumab treated animals that died with more severe CNS findings had longer times from treatment to death, and from challenge to death, than animals with no CNS findings. This finding is not seen in the placebo group, where these same times of

treatment to death and challenge to death in the 1 animal with high pathology overlapped with the animals with low pathology. Furthermore, when all these times are compared across groups, as shown in Figure 7.4.1-1 below, there is significant overlap in the various times for animals with low and high pathology levels.

Figure 7.4.1-1: FDA Comparison of time from challenge to death by treatment and pathology grade in Study 724-G005829





Note: Red = High Pathology Level
Gray = Low Pathology Level

The same results are seen with the pivotal rabbit study. While the raw data is not presented, the corresponding figures are shown below (Figures 7.4.1-3 and 7.4.1-4).

Figure 7.4.1-3: FDA Comparison of time from challenge to death by treatment and pathology grade in Study 682-G005758 (NZW rabbits)

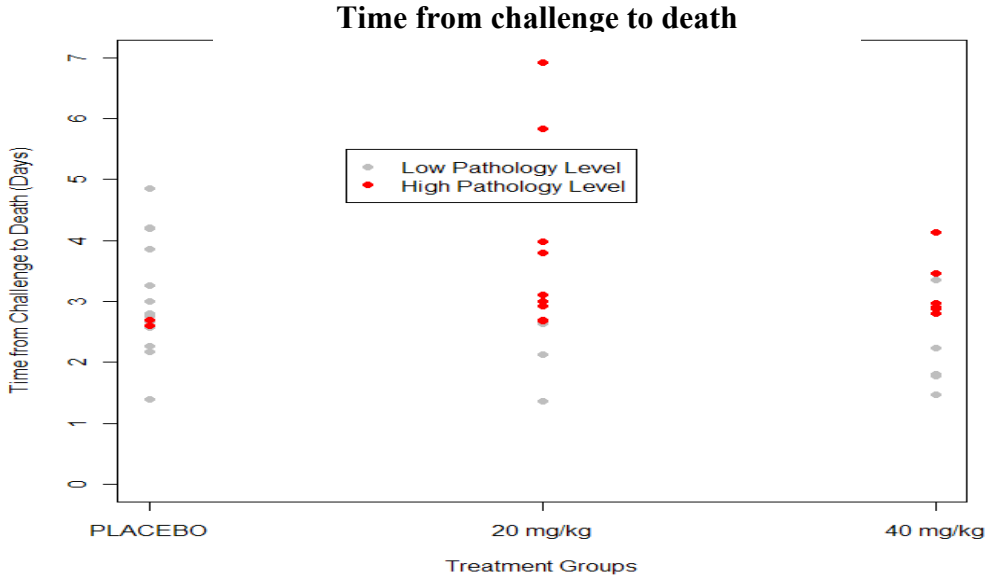
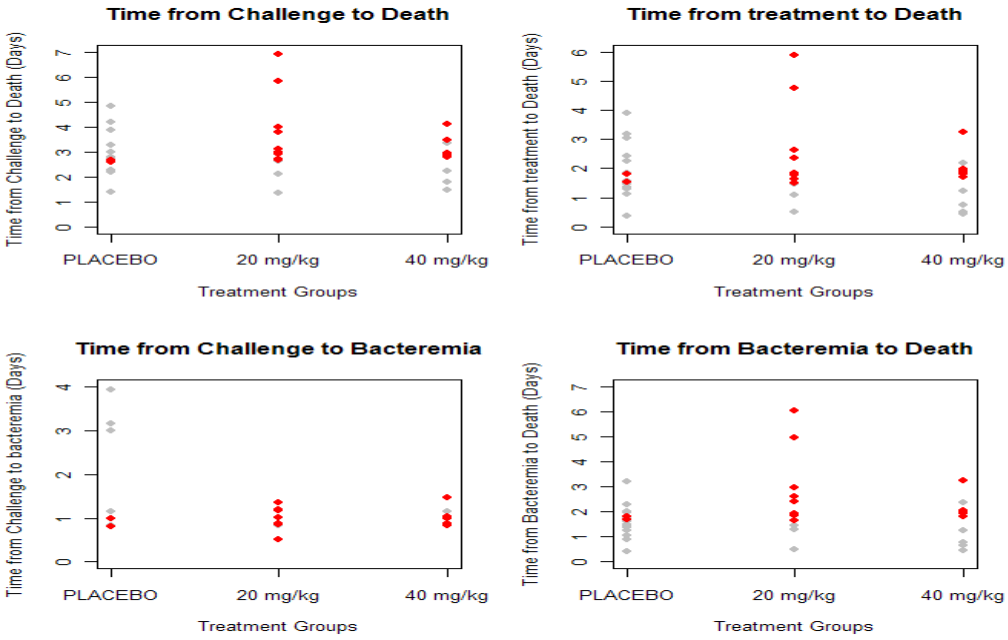


Figure 7.4.1-4: FDA Comparison of various time analyses by treatment and pathology grade in Study 682-G005758 (NZW rabbits)



Note: Red = High Pathology Level
Gray = Low Pathology Level

In summary, placebo animals with comparable survival times to those in the active treatment groups did not have CNS findings. Therefore longer survival time does not account for the increased CNS findings observed in raxibacumab treated animals. This suggests a possible study agent-disease interaction, with CNS findings associated with raxibacumab treatment in those animals which develop anthrax disease.

7.4.2 Exposure-response CNS findings

As stated previously, in the pivotal animal studies, animals that were treated with raxibacumab and died exhibited a higher incidence of histopathologic findings in the brain versus placebo treated animals, as presented in Figure 7.4.2-1. Histopathologic findings were also of higher severity in raxibacumab treated animals versus animals receiving placebo treatment, as presented in Figure 7.4.2-2. The raxibacumab 20 mg/kg dose group had a higher incidence and severity of CNS findings versus the 40 mg/kg group, suggesting an absence of clear dose-response relationship for brain histopathology.

Figure 7.4.2-1 Histopathology Findings by Treatment in Rabbits and Monkeys that Died

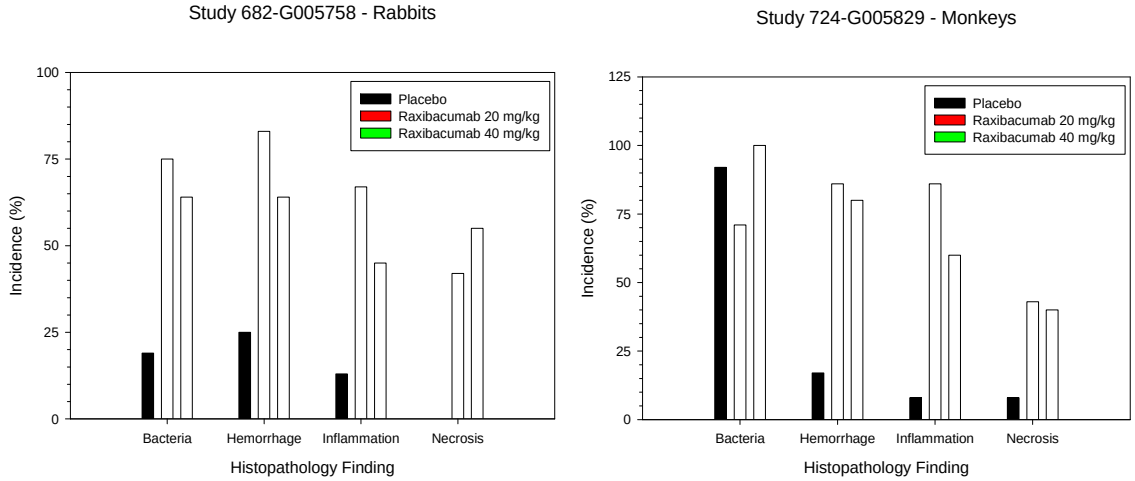
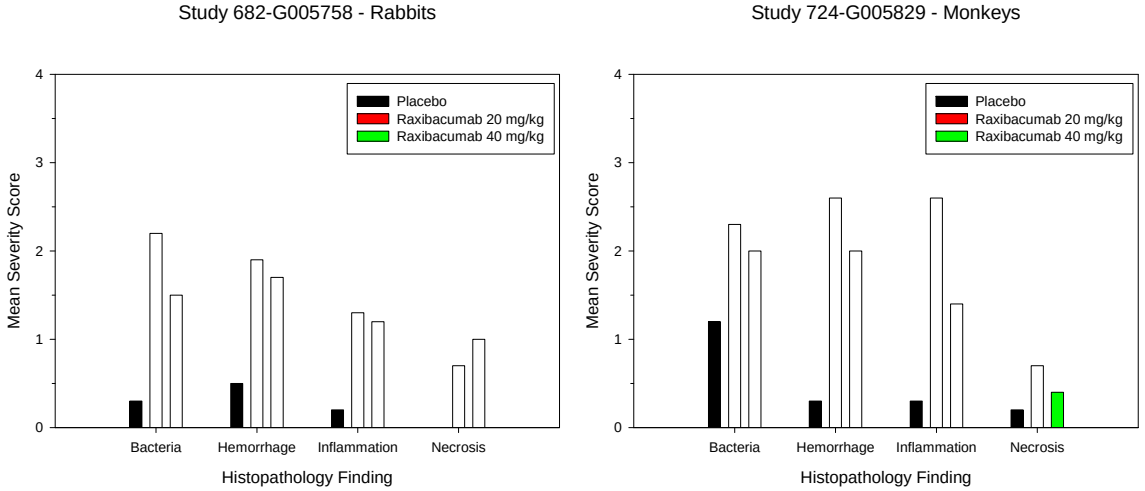


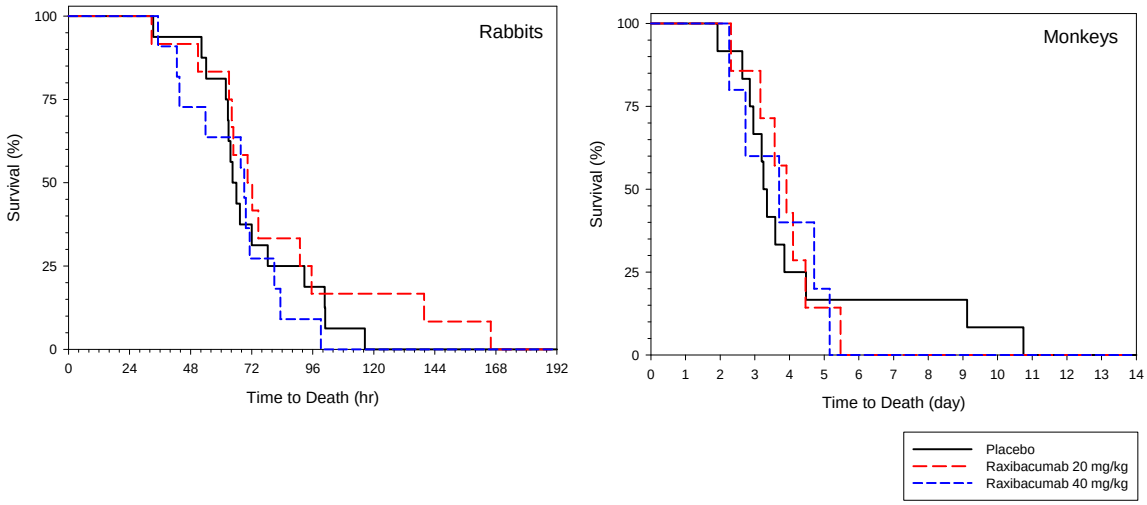
Figure 7.4.2-2 Severity of Histopathology Findings by Treatment in Rabbits and Monkeys that Died



Grading scale is as follows: Grade 1, minimal representing the least detectable lesion; Grade 2, mild representing an easily discernable lesion unlikely to have biological relevance; Grade 3, moderate representing a change affecting a large area of the represented tissue that had the potential to be of some relevance; and Grade 4, marked representing a lesion that approached maximal.

A potential hypothesis was proposed by the applicant to explain the finding that adverse CNS findings were more prevalent in animals that received raxibacumab and died versus animals that received placebo and died is that animals that received raxibacumab survived longer and brain lesions increased over time. Figure 7.4.2-3 shows percent survival and survival time by raxibacumab dose for rabbits and monkeys that died in the pivotal studies. The survival plots show that in rabbits that died, placebo animals have comparable survival times versus animals that received 40 mg/kg of raxibacumab. In monkeys that died, animals that received placebo lived longer than those receiving raxibacumab. Thus, the potential for raxibacumab treatment to result in adverse CNS findings is not likely to be related to prolonged survival time.

Figure 7.4.2-3 Time to Death in Rabbits and Monkeys That Died



In addition, time to death by exposure quantile was examined to determine if in animals that died, higher raxibacumab exposure led to longer survival times. Figures 7.4.2-4 and 7.4.2-5 show percent survival and survival time by quantiles of exposure (Cmax and AUC) for rabbits and monkeys that died, respectively. In rabbits that died, animals in the lower Cmax and AUC quantiles appeared to live longer than the other groups and placebo, but in monkeys there was no discernable difference between survival times for the higher and lower quantiles of exposure. In monkeys, the placebo group exhibited a longer survival time compared to the raxibacumab groups. This suggests that in animals that died, the magnitude of raxibacumab exposure did not affect survival time.

Figure 7.4.2-4 Comparison of Time to Death in Rabbits by Quantile of Raxibacumab Exposure

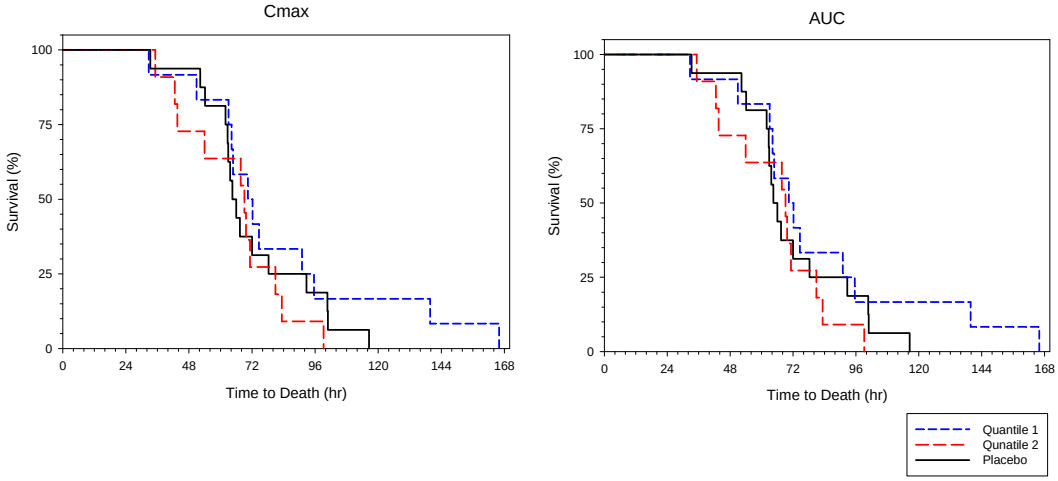
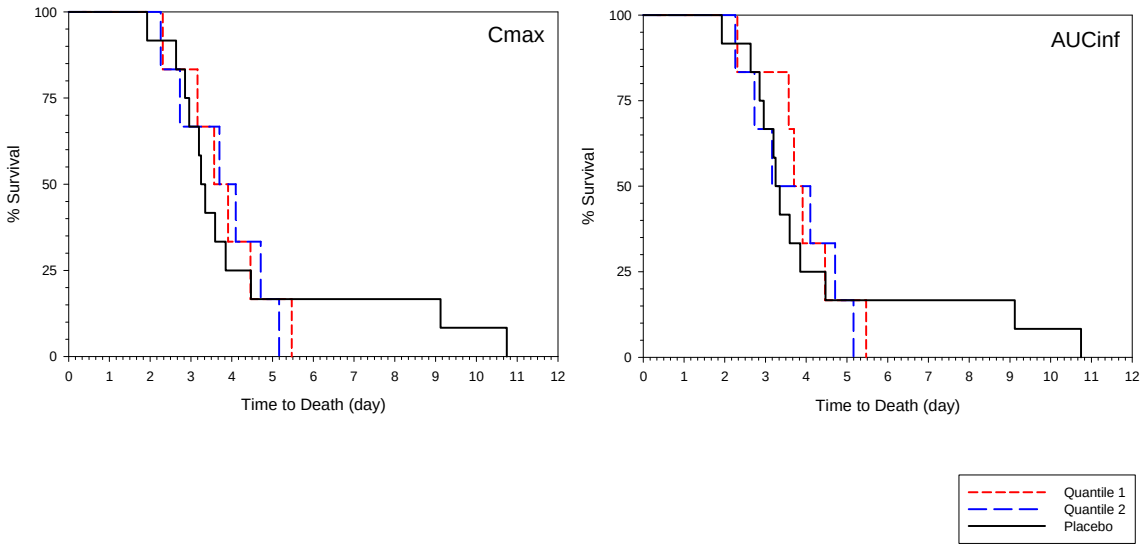


Figure 7.4.2-5 Comparison of Time to Death in Monkeys by Quantile of Raxibacumab Exposure

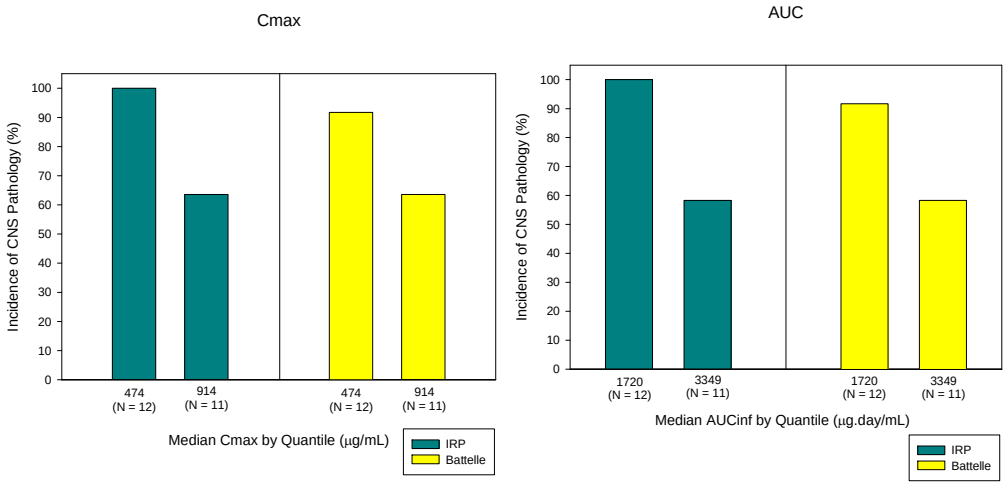


In rabbits, a lower incidence of CNS pathology was observed in higher quantiles of exposure for both Cmax and AUC, as presented in Figure 7.4.2-6. In addition, a lower incidence of bacteria, hemorrhage, and inflammation, but not necrosis, was observed with higher exposures (both Cmax and AUC).

In monkeys, all but one monkey (11/12, 91.7%) that received raxibacumab treatment exhibited CNS findings on necropsy (based on Battelle assessment; all raxibacumab monkeys that received raxibacumab and died had CNS pathology in the independent pathologist's assessment). In monkeys, a lower incidence of hemorrhage and inflammation with higher exposures (primarily for Cmax) is suggested. Conversely, higher exposure had a higher incidence of bacteria in the CNS for both Cmax and AUC. The incidence of necrosis did not appear to be related to magnitude of exposure in monkeys.

Due to the small numbers of animals that exhibited specific pathology findings, no definitive conclusions about exposure-response for bacteria, hemorrhage, inflammation, or necrosis could be made.

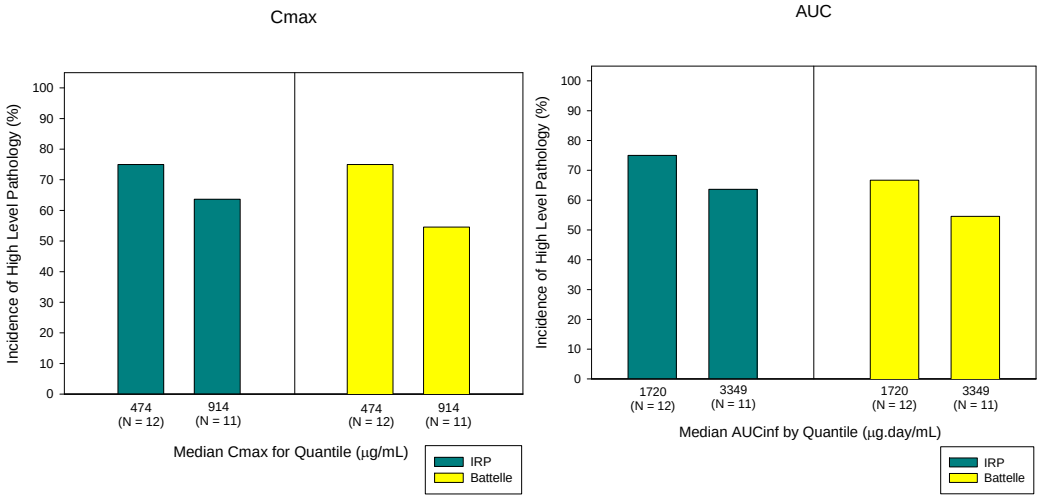
Figure 7.4.2-6 **Comparison of Incidence of CNS Pathology in Rabbits that Died by Quantile of Raxibacumab Exposure**



Cmax quantile ranges: Quantile 1 (342 – 543), Quantile 2 (624 – 1166)
AUCinf quantile ranges: Quantile 1 (1380 – 2144), Quantile 2 (2971 – 3978)
IRP, readings performed by independent pathologist review
Battelle, readings performed by board-certified pathologist at study site

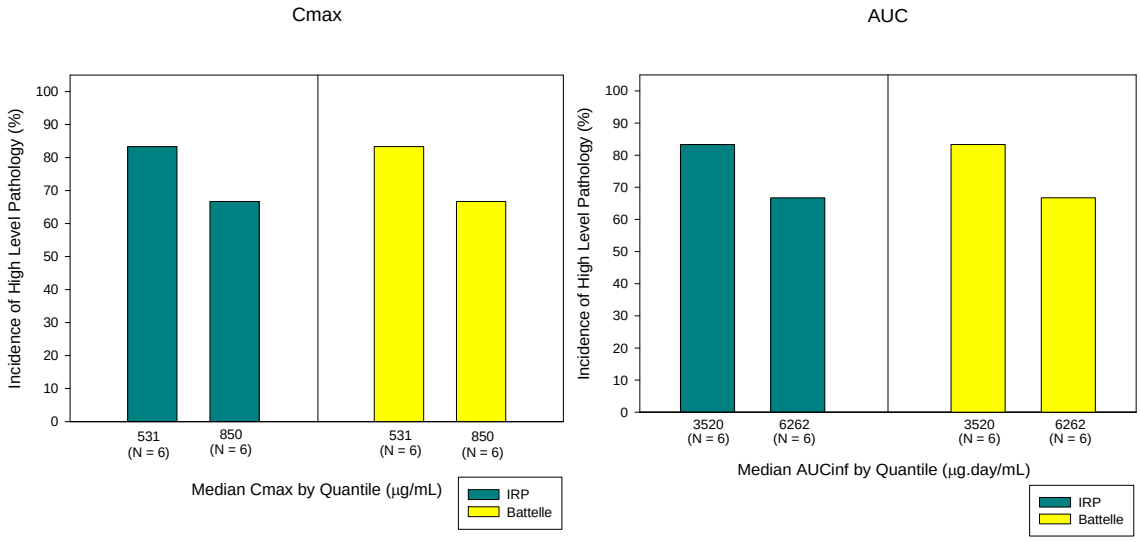
As presented in Figures 7.4.2-7 and 7.4.2-8, a lower incidence of high level CNS pathology was observed with higher quantiles exposures in both rabbits and monkeys. No clear relationship between exposure and response for CNS pathology grade severity can be discerned since these differences between grades were attributed to small numbers of animals.

Figure 7.4.2-7 **Comparison of Incidence of High Level (Grades ≥ 3) CNS Pathology in Rabbits that Died by Quantile of Raxibacumab Exposure**



Cmax quantile ranges: Quantile 1 (342 – 543), Quantile 2 (624 – 1166)
AUCinf quantile ranges: Quantile 1 (1380 – 2144), Quantile 2 (2971 – 3978)
IRP, readings performed by independent pathologist review
Battelle, readings performed by board-certified pathologist at study site

Figure 7.4.2-8 Comparison of Incidence of High Level (Grades ≥ 3) CNS Pathology in Monkeys that Died by Quantile of Raxibacumab Exposure



Note: A lower incidence of high level CNS pathology was observed in the higher quantiles of exposure, but this finding can be attributed to one animal (N = 4 in the lower quantile versus N = 5 in the higher quantile).
IRP, readings performed by independent pathologist review
Battelle, readings performed by board-certified pathologist at study site

8 Summary and Limitations of Efficacy and Safety for Raxibacumab

8.1 Efficacy

Four animal efficacy studies were conducted. Raxibacumab at 40 mg/kg IV was superior to placebo in the rabbit and monkey studies. In the monkey study, raxibacumab 20 mg/kg was also superior to placebo, but in the rabbit the efficacy of the 20 mg/kg dose was not superior to placebo. When given in combination with antimicrobials, the efficacy of the combination was high, but the efficacy of antimicrobials alone was also high, raising the question whether the animal model adequately reflects the findings from patients with inhalational anthrax whose response to antimicrobials approximates the 55% seen during the 2001 spread of anthrax spores in the mail.

Despite the superiority of raxibacumab to placebo in the efficacy studies using the animal models that have been carefully and extensively tested and characterized, it is still unknown how well these models and results predict efficacy in humans.

There are several limitations to the efficacy analyses of pivotal and combination animal studies and in animal models themselves. First, the time of intervention is likely to differ between animals and humans. In the experimental settings, animals were closely monitored for either an elevation in temperature (rabbits) or a positive serum PA (rabbits and Cynomolgus monkeys), and once detected, a therapeutic intervention was delivered. Humans may have delayed presentation to the healthcare setting or be given alternative diagnoses prior to the definitive diagnosis of anthrax being made. As the effects of delayed administration of raxibacumab after the onset of clinical symptoms has not been studied in the animal models, it is unclear how long raxibacumab administration can be delayed and still provide survival benefit.

Second, the combination efficacy studies demonstrated very high efficacies (nearly 100%) of levofloxacin in NZW rabbits and ciprofloxacin in cynomolgus monkeys, respectively. In contrast, during the 2001 anthrax attacks 5 of the 11 people who developed inhalation anthrax died despite best available treatment.

Third, the conditions of an animal experiment do not include any supportive care that human patients with inhalational anthrax will receive in a healthcare or clinical trial setting, including but not limited to mechanical ventilation, fluid resuscitation, pleural fluid drainage, dialysis, etc.

Therefore, these limitations need to be taken into consideration when evaluating and extrapolating the efficacy of raxibacumab seen in the animal models of anthrax disease to humans.

8.2 Safety

Animal Models

With respect to the pivotal efficacy studies and CNS findings, the main limitation was that survivors were not sacrificed and therefore no brain histopathology was available to compare to animals that died. In the pivotal efficacy studies evaluating raxibacumab versus placebo, surviving rabbits were euthanized and disposed of, while surviving NHP were observed for the duration of the study and confined to the Biosafety Level 3 (BL3) laboratory husbandry for 30 days post exposure, then downgraded to a BL2 husbandry for an additional 60 days and after were released into the colony in generally good health to be used in other experiments.

Although survivors were sacrificed in the combination levofloxacin/raxibacumab rabbit study, the high efficacy of the fluoroquinolone in this study limited the number of animals that died from anthrax in the active treatment arms. While all placebo animals had microscopic findings consistent with anthrax, only one animal in an active treatment group died of anthrax (rabbit K99203, levofloxacin group; note rabbit K99246 in the levofloxacin/raxibacumab group died of a gavage accident). Although it was reassuring that none of the surviving animals in the two treatment arms exhibited CNS pathology attributable to anthrax, all treated animals received a fluoroquinolone in this study unlike the pivotal efficacy studies. Therefore, additional information to further investigate the CNS findings observed in the pivotal studies could not be obtained.

Similar findings were noted in Study 789-G923702 (ciprofloxacin and raxibacumab in Cynomolgus monkeys). No animals in the ciprofloxacin group died during the initial 28 day time period (monkey C30988 died at 36 days from left leg arterial thrombosis). Only one animal in the ciprofloxacin/raxibacumab treatment group died of anthrax disease (monkey C31142). The other death in this group was due to a gavage error (monkey C24791). None of the surviving animals were sacrificed for CNS histopathologic analysis. As with the rabbit study, additional information to further investigate the CNS findings observed in the pivotal studies could not be obtained.

Human volunteers

In human volunteers, the most common adverse reactions were headache, whereas upper respiratory infections and gastrointestinal events were similar in the raxibacumab and placebo arms. A noteworthy findings was seen in study HGS1021-C1064, when 6/27 (22%) of volunteers without prior administration of diphenhydramine developed rash and urticaria after infusion of raxibacumab (the M11 to-be-marketed formulation). As a result of this finding, patients are to receive diphenhydramine pretreatment before raxibacumab infusion.

With respect to clinical safety, a safety database of 326 subjects can exclude events that occur with a 1% or greater frequency, but cannot exclude events, including a SAE or fatal event, occurring at less than 1% frequency. In addition, as the safety database consisted only of healthy volunteers, any possible study agent/disease interaction could not be assessed. While CNS AEs were reviewed in healthy volunteers, it appears from the animal models that systemic anthrax disease must be present for CNS pathology to be observed. A review for CNS safety in humans was therefore limited.

Given that the safety evaluation involved adult subjects, other limitations with respect to safety include the exclusion of pediatric subjects and other special populations (pregnant patients, and patients with renal and hepatic dysfunction) from the safety database. Similarly, non-white subjects represented 28% of the safety database, while subjects greater than 65 years of age represented 6.4% of subjects; the implication of these limitations need to be taken into consideration when assessing how generalizable the results are to such populations.

9. Points for Discussion

Based on the information regarding the natural history of inhalational anthrax (disease due to *Bacillus anthracis*) in different species, rabbits and monkeys, the pharmacokinetics, mechanism of action, efficacy and safety of raxibacumab in the animal studies, and the safety of raxibacumab in normal volunteers:

(1) Does the evidence from the pivotal animal studies support the conclusion that raxibacumab at 40 mg/kg is reasonably likely to have efficacy in humans?
If not, what additional studies should be conducted?

(2) Does the evidence from the pivotal animal studies and human safety studies support the conclusion that the benefits of raxibacumab therapy outweigh its risks for the treatment of inhalational anthrax?
If not, what additional studies should be conducted?

In animal models (both rabbit and monkey) of inhalational anthrax disease, a single dose of raxibacumab 40 mg/kg IV given in combination with antimicrobial therapy (levofloxacin in rabbits, ciprofloxacin in monkeys) resulted in similar observed efficacy as antimicrobial alone.

(3) Does the evidence provided support the conclusion that raxibacumab will not diminish the anticipated efficacy of antibiomicrobials in inhalational anthrax?
If not, what additional studies should be conducted?

(4) Given the high efficacy of the antimicrobial arms in the rabbit (95%) and monkey (100%) studies the added benefit of raxibacumab to antimicrobial could not be determined. Should evidence be requested that raxibacumab makes a contribution to the efficacy over the antimicrobial alone (in rabbit and monkey animal models)? If yes, what types of additional studies should be requested and conducted?

The safety of raxibacumab 40 mg/kg infused IV was assessed in healthy normal volunteers, who also received diphenhydramine.

(5) Are there additional comments or further recommendations for safety evaluation in humans? If yes, what are these recommendations?

Based on the information provided from the animal models of disease and human volunteers, what information would be useful to include in product labeling, if the product is approved:

(6) Efficacy of raxibacumab including raxibacumab use alone or in combination with antimicrobials?

(7) Other information, including safety information, specific information for patients?

For products approved under the Animal Rule, applicants need to agree to conduct field studies in the event there are patients with inhalational anthrax and the product is used. FDA can also ask that applicants commit to conducting additional studies that are needed.

(8) What additional studies should be requested?

10 Appendices

The following appendices are attached:

10.1 Appendix -- 1: Experimental Assays

10.2 Appendix – 2: Anthrax Disease – Natural History

10.3 Appendix -- 3: List of Studies conducted

10.1 Appendix-1: Experimental Assays

Electrochemiluminescence Assay:
A screening and a quantitative ECL assay were designed for the purpose of detecting PA, as a biomarker, in **serum** from infected rabbits and monkeys to use as a trigger for intervention in efficacy studies. **Plasma** samples were used in the rabbit study that evaluated the efficacy of raxibacumab in combination with levofloxacin.

The principle and methodology of the ECL assay were based on that of ELISA with rabbit polyclonal anti-PA antibodies tagged either to biotin or a Sulfo luminescent compound (Figure 10.1-1).

Figure 10.1-1. The principle of the ECL assay[23]

pAb = polyclonal anti-PA antibody

The lower limit of detection (LOD) and lower limit of quantitation (LOQ) of the assays in rabbits and monkeys are summarized in Table 10.1-1. Overall, the results suggest that the ECL assay has a high level of sensitivity. However, there are shortcomings in the ECL tests in both rabbits and monkeys. Common to both are the inadequacies related to specificity and precision.

[23] Human Genome Sciences Inc., Report no. TR-21-08-003, p 7.

Table 10.1-1. Cutoff limits and variability ranges for Rabbit and Monkey ECL assays for detection of PA				
Test	**LOD (ng/mL)**	**LOQ (ng/mL)**	**ULOQ (ng/mL)**	**% Coefficient of Variation***
Rabbits:				
Screening** (Serum)	0.4	NA	NA	9 - 24 %
Quantitative (Serum)	0.114	0.17	20.5	7 - 38 %
Screening (Plasma)	0.5	NA	NA	13 - 22 %
Quantitative (Plasma)	NA	0.14	125	6 – 15 %
Monkeys:				
Screening (Serum)	1	NA	NA	19 – 39 %
Quantitative (Serum)	0.065	0.065	144.5	10 – 19 %

LOD = Lower limit of detection; **LOQ** = Lower limit of quantitation;
ULOQ = Upper limit of quantitation.
*Total (%CV) for positive control samples and represents data from both HGS and Battelle laboratories and acceptable limits were set based on a publication by Findlay *et al*., 2000[24].
**15% normal rabbit sera positive at Battele laboratory

(1) Specificity:
(i) Cross reactivity:
In the ECL assay for PA in rabbit serum and plasma as well as monkey serum, the testing was limited to edema factor at a concentration of 5.0 ng/mL. The testing of cross-reactivity against only EF of *B. anthracis* is inadequate. Other possible sources of cross-reactivity or nonspecific binding such as with bacterial species other than *B. anthracis* were not evaluated.

(ii) Testing of Naïve animals:
The shortcoming of specificity testing is further highlighted in the screening ECL assay for PA in rabbit serum when 7/46 (15%) normal rabbit serum samples showed counts of ECL values higher than the limit of detection (Table 10.1-2). In the rabbit quantitative PA assay 4/30 (13 %) of normal rabbits also gave positive ECL counts. The reasons for these false positive results in normal rabbit sera were not provided. Although the false positive results were lower in monkeys (Table 3), it is important to note that these results are based on high acceptance criteria ≤ 20 (≤25% at the lower limit of quantitation) and variability.

[24] Findlay *et al*., 2000, J Pharm,aceutical Analysis, 21: 1249

Table 10.1-2: Specificity of ECL Assays in rabbits and monkeys[a]

Animal Species		Number of Animals positive by ECL Assay	
		Battelle	HGS
Rabbits:			
Screening Assay	Serum	7/46 (15%)	2/46 (4.3%)
Quantitative Assay	Serum	NT	4/30 (13%)
Screening Assay	Plasma	1/35 (2.9%)	1/35 (2.9%)
Quantitative Assay	Plasma	NT	2/28
Monkeys:			
Screening Assay	Serum	0/35	0/36
Quantitative Assay	Serum	NT	0/12

[a] Results based on %CV based on acceptance criteria of ≤ 20 (≤ 25% at the lower limit of quantitation)
False positive results detected in background analysis using serum or plasma from animals not infected with B*acillus anthracis.*

Although the screening assay in serum was conducted at both the Battelle and HGS Laboratories, the results of the screening PA assay conducted at the Battelle laboratory showed higher variability and was used as a biomarker for trigger for intervention in efficacy studies.

Some of the serum samples from rabbits and monkeys were positive by the screening and quantitative ECL assay prior to enrollment in the efficacy studies (Table 10.1-3).

Table 10.1-3. Overall Positive Baseline Serum PA Results

Study	Positive Results by Assay	
	Screening PA[a]	Quantitative PA
NZW Rabbit:		
615-N104504: Animal Model Characterization	Not tested	0/8
682-G005758: Pivotal Efficacy	2/52 [b]	3/52
723-G005835: Levofloxacin only	0/27	1/27
781-G923701: Raxibacumab + Levofloxacin**	0/46	2/46
Cynomolgus Monkeys		
685-G005762: Animal Model Characterization	Not tested	1/8
724-G005829: Pivotal Efficacy	0/40	0/40
789-G923702: Raxibacumab Raxi + Ciprofloxacin	2/40	3/40[3]

[a] Based on testing at Battelle laboratories
[b] 24/52 samples were considered test failures due to either QC failures or high CVs (based on acceptance criteria of ≤ 25%[1]
[3] Two animals had to be retested due to QC failure , 3 extra animals tested.
**Based on testing of plasma samples

(2) **Precision:**
The precision in all the ECL assays for PA measurement was poor with the percentage coefficient of variation (CV) unacceptably high. For example, the mean %CV which was used to measure the PA spikes in the screening rabbit serum assay at the Battelle Laboratories ranged from 16 to 24%. The %CVs at the Battelle laboratories were higher than those at the HGS laboratory (Tables 10.1-4 and 10.1-5).

For the monkey screening serum sample, HGS established the acceptability criteria for the positive and negative controls as CV ≤ 25% and excluded samples that resulted in a % CV > 30 from the data analysis which is inappropriate. The reasons for that are unclear.

In the screening assay there was considerable variability in intra- and inter-laboratory performance by run and by day. For example, a 0.5 ng/mL spike run in triplicate by operator 2 on Day 1 at HGS resulted in percentage sample increases of 51%, 29% and 66% (Tables 10.1.4 and 10.1.5). For the same spike run in duplicate by operator 2 on day 1, one of the results could not be used while the other showed a 21% increase. For tests performed at HGS, the % CV was 31% for 0.5 ng/mL of PA, 24% for 1 ng/mL and 23% for 2.0 ng/mL. The %CVs for tests done at Battelle were 33 %, 29 % and 19 %, respectively, for the same concentrations of PA. Overall, the % CV appeared too high to provide the level of precision that is required for a diagnostic test. Additionally, with regard to controls, there were a number of instances when the calibrators were used as controls.

Table 10.1-4: Cumulative results of eight PA tested at HGS[25]

PA (ng/mL)	Mean	SD	CV (%)	% Increase
0	306	33.90	11.08	NA
0.4	459	47.66	10.38	50%
0.5	494	43.94	8.89	62%
0.6	542	55.49	10.23	78%
0.75	580	59.80	10.31	90%
1	624	72.31	11.59	104%
2	992	124.17	12.52	225%
5	2168	254.73	11.75	611%

Table 10.1-5: Cumulative results of eight PA spikes spikes tested at Battelle[25]

PA (ng/mL)	Mean	SD	CV (%)	% Increase
0	296	61.46	20.75	NA
0.4	448	74.26	16.59	51
0.5	505	82.67	16.38	70
0.6	573	127.82	22.32	93
0.75	610	136.23	22.31	106
1	658	138.17	21.00	122
2	1085	223.30	20.58	266
5	2489	595.66	23.93	740

The measurement of PA by either screening or quantitative ECL assays, as standardized, is not reliable and showed high variability and lack of specificity. Cure rates should be presented based on bacteremia and not PA positive findings by the ECL assay.

PCR

The Real-time PCR assays were well planned and executed. The pagA assay identified the presence or absence of the pOX1 plasmid containing the target gene sequences from *B. anthracis* DNA obtained from a clone of a pcDNA2.1 vector, and the amplicon used for the primers and probe set. The chromosomal assays ascertained that *B. anthracis* was present in the serum in which the plasmid was found, as such, that the plasmid came from *B. anthracis* and not another species, and the 18s assay quality controlled the DNA extraction process. Table 10.1-6 shows the criteria used for the determination of *B. anthracis* bacteremia by PCR. The %CVs are very low indicating a high level of precision. The major short coming of this assay was the need to provide proof of specificity. Once additional tests for specificity are performed (such as detection of *Bacillus* species other than *B. anthracis* and bacterial species other than *Bacillus* species) the Real-time assay can be used as a presumptive trigger for intervention. Evaluation of sensitivity to the detection of strains other than Ames would greatly enhance the utility of this assay.

[25] Human Genome Sciences Inc., Report no. TR-21-08-003, p 14 , 17.

Table 10.1-6: Criteria used for determining positive bacteremic sample by Real time PCR

Animal Species	Assay	LOD	Criteria for positive Result (Ct value)	Criteria for negative Result (Ct value)	Total (%CV) for positive control samples	Comments
Rabbit	pagA	15 copy	≤ 38 +	> 38	1.2 – 8.0	Cross-reactivity with other pathogens not tested
	Chromosomal	0.025 pg	≤ 38 +	> 38		
	18s *	0.125 ng	≤27	≤27		
Monkey	pagA	20 copies	≤ 36 +	> 36	0.8 – 2.5	Cross-reactivity with other pathogens not tested
	Chromosomal	0.1pg	≤ 36 +	> 36		
	18s	0.25 ng	≤27	≤27		
A sample with Ct value for 18s assay > 27 is unsuitable. Ct = Threshold cycle						

10.2 Appendix-2: Anthrax Disease – Natural History

Cynomolgus Monkey

Study design
This was a non-GLP study in eight healthy, adolescent to young adult, sexually mature *Macaca fascicularis* (7 males, 4.4 to 7.7 kg; 1 female, 3.1 kg). Note that the monkeys used in the pivotal efficacy studies were juveniles. The objectives of the study were to:

a) determine the time to onset of abnormal values in physiological and clinical signs,
b) obtain a better understanding of disease progression in cynomolgus monkeys post-anthrax spore exposure, and
c) identify a parameter(s) that indicates an optimal window of time for therapeutic intervention.

All monkeys had survived a previous infection with monkey pox virus. Monkeys were negative for *Mycobacterium tuberculosis*, *Cercopithecine herpesvirus* 1 (Herpes B virus), simian retrovirus, and Simian T-Lymphotrophic Virus-1 (STLV-1). Prior to study initiation, all monkeys had negative tests for anti-PA antibodies by ELISA and toxin neutralization assay (TNA). Monkeys had telemetry transmitters implanted from previous experiments. Telemetry parameters measured included temperature, physical activity, blood pressure, heart rate, pulse pressure, and respiratory rate. Baseline values were obtained for all monkeys by recording values starting about 11 days prior to study initiation.

The dose of *B. anthracis* Ames strain spores used was based on the LD_{50} determined previously by USAMRIID and Battelle Laboratories in juvenile cynomologus macaques.[2121] In the Vasconcelos study, groups of juvenile monkeys were exposed to aerosols containing 4.56×10^4 to 2.94×10^6 CFU of the Ames strain of *B. anthracis* spores in a head-only aerosol exposure chamber. All animals were culture-positive for *B. anthracis* and died within 10 days (range 2 – 10 days) of aerosol exposure, with a tendency for those receiving higher doses to succumb more quickly than those receiving lower doses. All monkeys exposed to at least 2.0×10^5 CFUs died within 4 days of exposure and the LD_{50} dose was determined to be 6.18×10^4 CFU.

The applicant used a target dose of *B. anthracis* Ames strain spores of 200 LD_{50}. The average aerosol exposure was 260 ± 108 x LD_{50} (range 167 to 451 x LD_{50}). The MMAD for challenge material aerosols was 1.06 µm. Note that at a particle size of 1-2 µm there are relatively more particulates deposited in nonhuman primate lungs than in humans, and the overall distribution of particles within the respiratory tract and stomach is about equal.[26] Although humans and nonhuman primates are more resistant than ruminants to GI anthrax, the possibility of other routes of infection leading to systemic disease cannot be ruled out.

Temperature was monitored by telemetery every hour. Blood samples were collected every six hours until 72 hours post-infection (PI) and at days 4, 5, 6, 7, 8, 14, 21, and 30 days PI for culture, detection of PA, and *B. anthracis* PCR. Animals were not followed for bacterial burden in tissues. Cultures were performed by directly inoculating 10 to 40 µL of whole blood onto a

[26] Cheng YS *et al*. Lung deposition of droplet aerosols in monkeys. 2008. Inhal. Toxicol. 20(11): 1029-36.

blood agar plate. All plates were incubated for a minimum of 48 hours at 37 ± 2° C. Identification of resulting growth as *B. anthracis* was determined by colonial morphology and hemolytic reaction. Sera were collected for detection of PA by the quantitative ECL assay and the presence of neutralizing PA antibodies by TNA. Animals were followed for up to 30 days PI. Terminal samples were taken, when possible, from any animal found dead or just prior to euthanasia if the animal was moribund. Gross necropsies were performed on all monkeys that died or were euthanized but systematic, comprehensive, necropsies were not done. Survivors were not necropsied.

Outcome

Measurement of temperature increase in cynomolgus monkeys was confounded by the diurnal temperature patterns typical of this species. Most (7/8) animals had a breakdown or loss in the ability to regulate their diurnal body temperature patterns post-challenge and temperature increases were transient and erratic. Consequently, temperature increase was not a reliable indicator of the onset of systemic disease.

The results of the major parameters measured are shown in Table 10.2-1. Two of eight monkeys survived inhalational anthrax. The infection was documented by culture, PCR, serum PA concentrations, and development of anti-PA antibodies. The reasons for their survival are unknown. The monkeys were not necropsied.

In the animals that died, the mean time to death was 116 ± 27 hours (4.8 ± 1.1 days) which is comparable to that reported previously (4.1 ± 2.3 days) by Vasconcelos *et al*.[21] All eight animals were bacteremic (by culture) by 48 hours PI (range 30-48 hours; median 40 hours). In nonsurvivors, once an animal became bacteremic, the blood remained culture positive until the animal died.

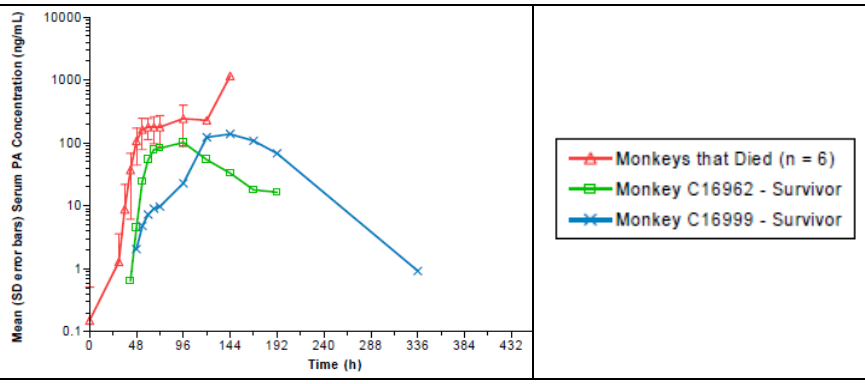
Culture was more sensitive in detecting bacteremia than either PCR or the quantitative ECL assay. At 30 hours PI, 4/8 monkeys had positive cultures, 2/8 monkeys had positive PCRs, and 3/8 monkeys were positive by quantitative PA/ECL assay. Overall, the time to first positive result for the PCR assay agreed with culture results in 5/8 monkeys. The time to first positive result for the PA/ECL assay agreed with culture in 6/8 monkeys, but the high variability seen with the quantitative ECL assay indicated that it should not be used as a trigger for intervention or for evaluating efficacy. Baseline PA measurements were not done.

Table 10.2-1. Characterization of Cynomolgus Monkey Model of Inhalation Anthrax: Summary of Events							
Animal ID	**Sex**	**Inhaled Dose (CFU x 10^7)**	**LD_{50} Dose**	**Time to Positive Test (hours)**			**Time to Death (hours/days)**
				Culture	**PCR**	**Quantitative PA / ECL**	
C16984	M	1.03	167	30	36	30	86 / 3.6
C17003	M	1.51	244	30	30	30	93 / 3.8
C17073	F	2.79	451	30	30	30	106 / 4.4
C16986	M	2.54	411	36	36	36	114 / 4.8
C16939	M	1.26	204	36	42	42	139 / 5.8
C16954	M	1.23	199	42	42	42	156 / 6.5
C16999*	M	1.27	205	48	48	48	NA
C16962*	M	1.24	200	30	42	42	NA
Mean ± SD	NA	1.61 ± 0.67	260 ± 108	35.3 ± 6.8	38.2 ± 6.4	37.5 ± 7.0	116 ± 27 / 4.8 ± 1.1
Median	NA	1.27	204	33	39	39	110 / 4.6

All monkeys were survivors of a monkey pox study. Monkeys were young adult animals.
M= Male; F = Female; NA = Not Applicable
PCR values are for an undiluted sample
* Survivor C16999 had a positive culture only at 48 hours and 5 days PI. Survivor C16962 had positive cultures at 30 hours and then had positive cultures from 48 hours through day 4 PI. After day 4, cultures were negative.

The kinetics of the concentration of PA in serum after infection was different in the six monkeys that died *vs*. the two monkeys that survived the infection (Figure 10.2-1). In monkeys that survived, the peak serum PA concentrations occurred later and were lower than in the animals that died. In survivors, serum PA concentrations reached an initial peak and then were negative (i.e., <0.065 ng/mL) within 21 days PI. In the non-survivors, serum PA concentration kinetics were triphasic (rise-plateau-rise). Note that specimens designated as collected at the time of death were sometimes collected after the animal had been dead for several hours, so terminal samples may have artificially high concentrations of PA since toxin would continue to be produced by replicating *B. anthracis* after the death of the animal.

Figure 10.2-1. Characterization of Cynomolgus Monkey Model of Inhalation Anthrax: PA Concentrations in Animals that Died (n=6) and Survivors (n=2)[27]



PA concentrations were determined by quantitative PA/ECL assay on stored samples.

[27] From Human Genome Sciences Study Report 685-G005762

Both of the surviving monkeys developed neutralizing antibodies after infection. Serum concentrations of PA were decreased at the times that neutralizing TNA titers were shown to be elevated, suggesting that the neutralizing antibodies included development of anti-PA antibodies that may help clear circulating PA.

Gross necropsies were done on 6/6 monkeys that died or were euthanized. Sections of target tissues collected for histology included brain/meninges, lungs, liver, spleen, kidney, and mediastinal lymph nodes but microscopic lesions were not evaluated in 4/6 monkeys that had gross lesions typical of anthrax. No samples were taken from the GI tract or mesenteric lymph nodes so possible lesions associated with GI anthrax were not evaluated. Because systematic, comprehensive necropsies were not done, it is unclear whether there were differences in lesions seen in these adult monkeys as compared to the lesions seen in the juvenile monkeys in the study by Vasconcelos *et al*[21] or in the juvenile monkeys used for the pivotal efficacy studies. Because there appears to be an age-related susceptibility and increased severity of disease in humans exposed with inhalational anthrax[28] characterization of the model would have been strengthened by systematic evaluation of all organs from these adult animals.

Histopathology was assessed only on the 2/6 monkeys that died that did not have gross lesions typical of anthrax (Table 10.2-2). Both monkeys had microscopic lesions consistent with anthrax in cynomolgus monkeys[28] including bacilli in tissues, edema, fibrin, hemorrhages, and suppurative inflammation in various organs. Monkey C16984 had more severe lesions, including lymphoid necrosis, in the bronchial and mediastinal lymph nodes. Both monkeys had about the same amount of lymphoid necrosis and suppurative inflammation in the spleen. Monkey C16984 had discolorations in two lung lobes that were associated with microscopically confirmed hemorrhage. The only gross lesion noted in monkey C17003 was red fluid accumulation in the ventral neck which was associated with hemorrhage upon microscopic examination of the tissue.

[28] Holty, J-E C, *et al*. Systematic Review: A century of inhalational anthrax cases from 1900 to 2005. 2006. Ann. Intern, Med. 144: 270-80.

Table 10.2-2. Characterization of Cynomolgus Monkey Model of Inhalational Anthrax: Confirmatory Gross and Microscopic Evaluation of Lesions in Two Cynomolgus Monkeys

ORGAN/Lesion	C17003	C16984
BRAIN:	Examined, unremarkable	Examined, unremarkable
KIDNEYS:	Examined, unremarkable	Examined, unremarkable
LIVER:	Examined, unremarkable	Examined, unremarkable
LUNG:	G2[2] = Adhesion, white, right diaphragmatic lobe.	G1 = Discoloration, dark, right intermediate lobe. G2 = Discoloration, dark, cardiac lobe
Bacteria	2	2
Edema	2	2
Hemorrhage (s)	0	3 = G1+G2
Inflammation, suppurative, alveolar	0	1
Pleural fibrosis (Incidental)	3 = G2	0
LYMPH NODE, BRONCHIAL		
Bacteria	2	2
Edema	2	2
Fibrin	1	0
Hemorrhage(s)	1	2
Necrosis, lymphoid	0	3
LYMPH NODE, MEDIASTINAL:		
Bacteria	1	2
Edema	2	2
Fibrin	0	3
Hemorrhage(s)	1	4
Necrosis, lymphoid	0	4
SKIN:	G1 = Fluid, ventral neck, red, 4 cc.	Non-protocol tissue not examined microscopically in C16984
Bacteria	1	
Hemorrhage	2 = G1	
SPLEEN:		
Bacteria	3	2
Necrosis, lymphoid	2	2
Inflammation, suppurative	1	1

Severity was scored as follows: 0 = no lesion; 1 = minimal lesion; 2 = mild; 3 = moderate lesion affecting larger proportion of the organ and likely to have clinical consequences; 4 = marked lesion, approaching maximal size/severity.
[2] G# indicates gross findings and includes findings seen during trimming of tissues for histopathology processing. Diagnoses correlating to the gross observations are listed with the corresponding G#.
From study report 685-G005762

In summary,

- Adult cynomolgus monkeys that had survived monkey pox experiments were used for the model characterization study. The published study by Vasconcelos *et al.*[21] and the pivotal monkey efficacy study used juvenile monkeys.

- In the two monkeys that survived, the infection was documented by culture, PCR, serum PA concentrations, and development of anti-PA antibodies. The monkeys were not necropsied. The reasons for survival are unknown.

- All of the monkeys that died (n =6) had gross or microscopic lesions consistent with anthrax but systematic, comprehensive, necropsies were not done. Thus, pathology cannot be easily compared to published data[21] or the pivotal efficacy study.

- Serum PA concentration kinetics were triphasic (rise-plateau-rise) but terminal samples may be artificially high due to the delay in collecting samples at necropsy.

- In monkeys that survived, the peak serum PA concentrations occurred later and were lower than in the animals that died.

New Zealand White Rabbit

Study design
This was a non-GLP study in eight, SPF, young adult, 3 to 5 kg, New Zealand White rabbits (4 male, 4 female) to

- characterize and evaluate markers for progression of disease such as clinical signs *(e.g.*, moribundity, respiratory distress, inappetence, decreased activity, seizures, and increase in body temperatures),
- presence of bacteremia by culture,
- detection of *B. anthracis* DNA by PCR,
- detection of serum PA, and
- determine hematological parameters after aerosol exposure to Ames strain *B. anthracis* spores.

The applicant used a target dose of 200 LD_{50} that was based on the LD_{50} dose in a previously conducted study by USAMRIID[18] in a NZW rabbit model of inhalational anthrax. In this study, the LD_{50} dose of the Ames strain of *B. anthracis* was 1.05×10^5 CFU. In rabbits weighing 2.5 to 3.5 kg, a particle size of 1-2 μm results in about 7% of the aerosol being deposited in the lower respiratory tract (lungs, bronchi, and trachea) and about 9.5% of the aerosol being swallowed.[29] Thus, the respiratory tract is not the only route of infection during aerosol exposures and this may be significant in rabbits since herbivores are highly susceptible to GI anthrax.

The animals were followed for clinical signs and symptoms of disease, and microbiologic and hematological parameters for up to 7 days PI (Table 10.2-3). From approximately 18 to 48 hours PI, rabbits were observed hourly (± 10 minutes) for clinical signs of illness. After 48 hours, rabbits were observed for abnormal clinical signs twice daily until Day 7. Baseline body temperatures from both transponder chips were measured for three days prior to the aerosol exposure and the baseline average temperature for each rabbit was calculated from all pre-challenge measurements. The shoulder chip location produced the least variable baseline readings and was used for all post-challenge temperature measurements. Post-challenge recording of temperature were done hourly (± 10 minutes) from approximately 16-72 hours PI and then subsequently twice daily until Day 7 PI.

[29] Raabe, OG, et al. Regional deposition of inhaled monodisperse coarse and fine aerosol particles in small laboratory animals. 1988. Ann. Occupational. Hyg. 32 (sup 1): 53-63.

Table 10.2-3. Blood Collection and Assay Schedule[30]

Hours post-challenge[1]	Blood Tube type/Approximate Blood volume	Bacteremia (Culture)	Bacteremia (PCR)	Serum PA level	CBC and CRP
-72	EDTA 1.0 ml				X
0 (Pre)	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
8	EDTA 0.5 ml	X	X		
12	EDTA 0.5 ml	X	X		
16	EDTA 1.5 ml	X	X		X
20	EDTA 1.5 ml	X	X		X
24	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
28	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
32	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
36	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
48	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
60	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
72	EDTA 1.5 ml + SST 1.0 ml	X	X	X	X
Terminal	EDTA 2.5 ml + SST 1.0 ml	X[2]	X	X	X[3]

Blood sampling times are approximate (± 10 minutes)
EDTA = Ethylenediaminetetraacetic acid anticoagulant; SST = Serum separator tube;
CBC =complete blood count. CBSs were not done on terminal blood samples.
CRP = C Reactive Protein

Blood samples were collected every four hours until 36 hours PI and at 48, 60, and 72 hours PI for culture, detection of PA, and *B. anthracis* PCR. Animals were not followed for bacterial burden in tissues. Cultures were performed, and *B. anthracis* identified, using the same methods as in the monkey model characterization experiment. No necropsies were done so lesions could not be compared to those reported by Zaucha *et al*. [18]

Outcome

The inhaled dose of *B. anthracis* ranged from 93-278 LD_{50}. One rabbit did not die from inhalational anthrax during the study period but the blood cultures, quantitative PA/ECL, and PCR were positive for *B. anthracis* when the rabbit was euthanized at 7 days PI.

Overall, 4/8 rabbits were dead by 3 days PI, and 7/8 animals died by 5 days (117 hours) PI (Table 10.2-4). The mean time of death was 95.5 ± 37.5 hours (3.9 ± 1.6 days) which is 24 hours longer than the 2.4 days that were reported by Zaucha *et al*.[18] Note that the times PI were calculated from the median challenge time for the entire exposure group so the reported times PI were not precise. Even when the inaccuracy of time PI is taken into consideration and the rabbit that survived for 14 days is excluded, the mean time to death is still longer (85.1 ± 25.4 hours or 3.5 ± 1.0 days) by > 24 hours than that reported by Zaucha *et al*.[18] The reason(s) for this

[30]Study HGS study report 615-N104504

discrepancy with the study by Zaucha *et al*. [18] is unknown but could be related to differences in methodology in growing the organism and preparing it for aerosolization, or the age and general health of the animals.

The time to first > 2°F temperature increase was highly variable (mean ± standard deviation, 31.1 ± 21.7 hours). In 4/8 rabbits, the time to first > 2 °F temperature increase occurred prior to the first indication of bacteremia. In the other 4 rabbits, the increase in temperature occurred after the onset of bacteremia. This suggests that temperature increase may not be a consistent indicator of early disease in rabbits and may not be a good trigger for treatment initiation.

Cultures were positive in 4/8 rabbits by 24 hours PI and in 7/8 rabbits by 36 hours PI. PCR agreed with cultural results (7/8) much better than did the quantitative PA/ECL assay (5/8). The median time for PCR positivity was 28 hours PI. Detection of bacteremia by PCR appeared to be a suitable rapid screening assay as it corresponded closely with culture results.

Cultures were positive earlier than serum quantitative PA/ ECL assay in 3/8 rabbits, and at the same time as the PA/ECL assay in 5/8 rabbits (Table 10.2-4). PA was detected in 3/8 rabbits by 24 hours and 7/8 rabbits by 36 hours. The variability noted in the quantitative PA ECL assay rendered it unsuitable for a rapid screening assay.

Table 10.2-4. Characterization of Rabbit Model of Inhalational Anthrax: Summary of Events

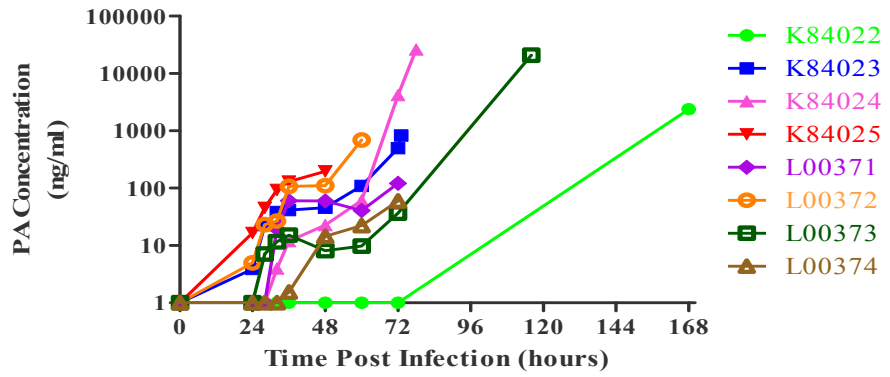
Animal ID	Sex	LD_{50} Dose	Time to Positive Test (hours)			Time to 2° F Temperature Increase (hours)	Time to Death (hours)
			Culture	Quantitative ECL	PCR		
K84022 *	M	152	168	168	168	79.4	>168
K84023	M	278	24	24	24	15	72.8
K84024	M	142	28	32	28	14	77.9
K84025	M	196	20	24	20	27.2	48.5
L00371	F	142	32	32	32	14.3	94.4
L00372	F	209	24	24	24	27.6	69.1
L00373	F	215	24	28	28	30.6	116.4
L00374	F	93	36	36	36	40.8	116.6
Mean ± SD (n=8)	NA	178 ± 57	44.5 ± 50.1	46 ± 49.5	45 ± 49.9	31.1 ± 21.7	95.5 ± 37.5
Median	NA	174	26	30	28	27.4	86.2

M= Male; F = Female;
NS = No Sample (animal found dead; no terminal culture); NA = Not Applicable
* Rabbit K84022 was euthanized at the end of the study (168 hours), at which time the blood culture was positive.

The time course curves for serum concentrations of serum PA are shown in Figure 10.2-2. There was an increase in PA concentration corresponding to the advent of positive cultures for *B. anthracis* and concentrations of PA increased with time PI. In general, there appeared to be a rise in concentrations up to about 36 hours PI, followed by a plateau in serum PA concentrations, after which the concentrations rose again. As mentioned above for the monkey natural history

study, these results should be interpreted with caution because of variability in the performance of the quantitative assay and the delay in collecting terminal samples at necropsy.

Figure 10.2-2. Characterization of Rabbit Model of Inhalational Anthrax: Serum PA Concentrations[30]



Rabbit ID	Time to Positive Culture (hours)
K84022	168
K84023	24
K84024	28
K84025	20
L00371	32
L00372	24
L00373	24
L00374	36

Serum PA concentrations were determined by quantitative PA/ECL assay.
Times Post Infection are generalized to facilitate graphing.

In summary,

- Of the eight infected rabbits, seven died by 117 hours PI with a mean time of death of 95.5 ± 37.5 hours. In the rabbit that survived, the blood cultures, quantitative PA/ECL assay, and PCR were positive when the rabbit was euthanized at 7 days PI.
- The mean time to death (most conservative estimate, 85.1 ± 25.4 hours) was >24 hours longer than that reported by Zaucha *et al.*[18] The reason for this is unclear.
- No necropsies were done so lesions could not be compared to published reports by Zaucha *et al.*[18]
- The time to first > 2°F temperature increase was highly variable (mean ± standard deviation = 31.1 ± 21.7 hours) suggesting that temperature increase was not a consistent indicator of early disease and may not be a good trigger for intervention.
- Cultures of blood were positive in 4/8 rabbits by 24 hours PI and in 7/8 rabbits by 36 hours PI. The median time to a positive culture was 26 hours.
- There was an increase in PA concentration corresponding to the advent of positive cultures for *B. anthracis* and concentrations of PA increased with time PI. In general, the PA concentrations were tri-phasic (rise-plateau-rise) but these results should be interpreted with caution because of variability in the quantitative assay and delay in collecting samples at necropsy.

10.3 Appendix-3: List of Studies conducted

10.3.1 Nonclinical toxicology/proof of concept studies list

Modified from HGS' BLA submission, section 2.6

Type of Study	Study Identifier	Title of Report	Objective of the Study
Pharmacology	AB50409.INF.0.010	PA mAb 587 binding kinetic parameters; BIAcore analysis	Binding kinetics (in vitro)
Pharmacology	AB50409.INF.0.008	PA binding to receptors expressed on the cell surface of CHO-K1, J774A.1 and human macrophages	Cell surface binding (in vitro)
Pharmacology	AB50409.INF.0.004	Inhibition of PA binding to receptor with PAmAb587	Inhibition of binding (in vitro)
Pharmacology	AB50409.INF.0.005	PAmAb587 inhibition of ^{86}Rb release in CHO-K1	Inhibition of binding (in vitro)
Pharmacology	AB50409.INF.0.006	PAmAb587 inhibition of ^{86}Rb release in primary human macrophage cells	Inhibition of binding (in vitro)
Pharmacology	AB50409.INF.0.007	PAmAb587 inhibition of murine macrophage cell killing	Inhibition of cytotoxicity (in vitro)
Pharmacology	TR-21-08-044	Binding of raxibacumab to PA produced by different *B. anthracis* strains	PA binding (in vitro)
Efficacy	AB50409.INF.0.011	Effect of PAmAb587 on survival of Fisher 344 rats challenged with anthrax lethal toxin: SC, IM, and IV administration of antibody 60 minutes prior to lethal toxin challenge	Rat PEP Efficacy
Efficacy	AB50409.INF.0.012	Effect of PAmAb587 on survival of Fisher 344 rats challenged with anthrax lethal toxin: SC, IM and IV administration of antibody 24 hours prior to lethal toxin challenge	Rat PEP Efficacy
Efficacy	AB50409.INF.0.013	Effect of PAmAb587 on survival of Fisher 344 rats challenged with anthrax lethal toxin: duration of protection	Rat PEP Efficacy
Efficacy	Cui et al (2005)	Late treatment with a protective antigen-directed monoclonal antibody improves hemodynamic function and survival in a lethal toxin-infused rat model of anthrax sepsis	Rat Efficacy
Tissue Cross-reactivity	1494-95	Cross-reactivity of PA mAb with human and cynomolgus monkey tissues ex vivo	Human and monkey
Tissue Cross-reactivity	IM1634	Cross-reactivity study of HGS1021 – raxibacumab with normal human, cynomologus monkey and New Zealand white rabbit tissues	Human, rabbit and monkey
PK	AB50409.INF.0.014	Pharmacokinetics of the PAmAb587 in BALB/c mice	Healthy mouse Raxibacumab PK
PK	AB50409.INF.0.015	Pharmacokinetics of the PAmAb587 in Fisher 344 rats	Healthy rat Raxibacumab PK
Toxicokinetics	AB50409.INF.034 to accompany Covance 6962-140	A toxicokinetic analysis of Covance Study No. 6962-140, "120-day toxicity study with PA mAb in cynomolgus monkeys"	Healthy monkey Raxibacumab PK
Toxicokinetics	AB50409.INF.038 to accompany Covance 6962-173	Pharmacokinetics of raxibacumab in pregnant New Zealand white rabbits following two intravenous injections given 7 days apart (GLP embryo-fetal toxicology study; Covance Study No. 6962-173)	Healthy rabbit Raxibacumab PK
Biodistribution	AB50409.INF.0.018	Biodistribution of 111In-labeled raxibacumab in rodents following IV or SC injection	Healthy mouse and rat Biodistribution
Toxicology	Covance 6962-140	120-day toxicity study with PA mAb in cynomolgus monkeys	Monkey chronic toxicology
Immunogenicity	AB50409.INF.025 to accompany Covance 6962-140	Immunogenicity of PA mAb following repeated SC or IV administration in cynomolgus monkeys (Covance Study 6962-140)	See above
Toxicology	Covance 6962-173	Intravenous study for effects on embryo-fetal development and toxicokinetics with raxibacumab in rabbits	Rabbit embryo-fetal toxicology
Immunogenicity	AB50409.INF.037 to accompany Covance 6962-173	Immunogenicity results for rabbit embryo-fetal raxibacumab toxicity study (Covance Study No. 6962-173)	See above

1 Unless otherwise indicated the content of the report provided in the BLA is identical to that previously submitted to FDA. 2 Serial number (SN) 058 was the HGS assigned SN for the submission dated 30 April 2008; however, this was recorded as FDA SN 057. (concluded)

10.3.2 Nonclinical Efficacy/Clinical Safety Studies List

Modified from HGS' BLA ubmission, section 5.2

Type of Study	Study Identifier	Title of Report	Objective of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	Number (Sex) of Subjects per group	Healthy Subjects or Diagnosis of Patients	Duration of Study
PK	AB50409.INF.0.016	Pharmacokinetics of raxibacumab in normal NZW rabbits following a single IV, SC, or IM injection	Healthy rabbit Raxibacumab PK	Randomized (non-GLP)	Raxibacumab Single dose 1 or 10 mg/kg, IV, IM, SC	2 M, 2 F (per group)	Healthy subjects	28 Days
See above	6962-137 to accompany AB50409.INF.0.016	Collection of Samples for Determination of PK of PA mAb after a single IV, SC, or IM dose to Rabbits	-	-	-	-	-	-
PK	AB50409.INF.0.017	Pharmacokinetics of raxibacumab in normal Cynomolgus monkeys following a single IV, SC, or IM dose	Healthy monkey Raxibacumab PK	Randomized (non-GLP)	Raxibacumab Single dose 1 or 10 mg/kg, IV, IM, SC	2 M, 2 F (per group)	Healthy subjects	42 Days
See above	6962-136 to accompany AB50409.INF.0.017	Collection of Samples for Determination of PK of PA mAb after a single IV, SC, or IM dose to Cynomolgus Monkeys	-	-	-	-	-	-
PK	PAM-NH-01.PK	Pharmacokinetic analysis of a phase 1 single-blind, placebo-controlled, single-injection, dose escalation study to evaluate the safety and pharmacokinetics of PA mAb (human monoclonal antibody to *B. anthracis* protective antigen) in healthy subjects	PH 1 Human Raxibacumab PK	Single-blind, dose-escalation, placebo controlled	Raxibacumab or placebo (raxibacumab formulation buffer) single dose 0.3, 1, and 3 mg/kg IM (gluteus maximus) 1 and 3 mg/kg IM (vastus lateralis) 1, 3, 10, 20, and 40 mg/kg IV	80 raxibacumab, 25 placebo	Healthy subjects	56 Days
PK	HGS1021-C1064.PK	Pharmacokinetic analysis of an open-label study to evaluate the pharmacokinetics and safety of raxibacumab (human monoclonal antibody to *B. anthracis* protective antigen) administered in combination with ciprofloxacin in healthy subjects	Ph 2/3 Human Raxibacumab PK Ciprofloxacin PK	Randomized (Groups 1 & 2), open-label	Raxibacumab single dose and/or ciprofloxacin for 7.5 days 500 mg ciprofloxacin PO doses q12h x 15 doses on days 0-7 + 40 mg/kg raxibacumab IV on day 5 (Group 1) 40 mg/kg raxibacumab IV on day 0 (Group 2) 400 mg ciprofloxacin IV q12h x 2 doses + 40 mg/kg raxibacumab IV on day 0 and 500 mg ciprofloxacin PO q12h x 13 doses on days 1-7	43 M, 45 F	Healthy subjects	56 Days
PK	AB50409.INF.0.027	Pharmacokinetic analysis for evaluation of the prophylactic and post-exposure efficacy of HGSI PA monoclonal antibody (PA mAb) against aerosolized anthrax in the rabbit model (Battelle Study No. 288-HGSIRAB)	Rabbit Pre-exposure prophylaxis					
PK	AB50409.INF.0.028	Pharmacokinetic analysis for evaluation of the prophylactic efficacy of raxibacumab (HGSI PA monoclonal antibody) against aerosolized anthrax in the monkey model (Battelle Study No. 290-N005433)	Monkey Pre-exposure prophylaxis					
PK	AB50409.INF.0.036	Raxibacumab pharmacokinetics and	Rabbit					

Type of Study	Study Identifier	Title of Report	Objective of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	Number (Sex) of Subjects per group	Healthy Subjects or Diagnosis of Patients	Duration of Study
		protective antigen kinetics during the evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the rabbit model (Battelle Study No. 682-G005758)	Therapeutic efficacy					
PK	AB50409.INF.0.040	Raxibacumab pharmacokinetics and protective antigen kinetics during the evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the monkey model (Battelle Study No. 724-G005829)	Monkey Therapeutic efficacy					
PK	AB50409.INF.0.039. 2	Levofloxacin pharmacokinetics and protective antigen kinetics during a pilot study evaluation of levofloxacin efficacy as therapeutic treatment against inhalation anthrax in the rabbit model (Battelle Study No. 723-G005835)	Rabbit Levofloxacin PK	Pilot, placebo controlled (non-GLP)	Levofloxacin 10, 25, and 50 mg/ml once daily x 3 gastric intubation/oral gavage or untreated control *Treatment was administered based on detection of increased temperature by individual animal	4 M, 4 F (+3 M control)	Anthrax challenged	21 Days
PK	AB50409.INF.0.043	Evaluating the efficacy of raxibacumab in combination with levofloxacin for post-exposure treatment in the NZW rabbit inhalational anthrax model (Battelle Study No. 781-G923701)	Rabbit Raxibacumab PK Levofloxacin PK	Randomized, placebo-controlled, double blind (GLP)	Placebo (raxibacumab buffer + WFI), raxibacumab buffer + levofloxacin 50 mg/kg, or raxibacumab 40 mg/kg + levofloxacin 50 mg/kg raxibacumab IV levofloxacin oral gavage *Treatment was administered based on detection of increased temperature or serum PA by individual animal	6 M, 6 F (placebo group) 10 M, 10 F (treatment groups)	Anthrax challenged	28 Days
PK	AB50409.INF.0.042	Ciprofloxacin and raxibacumab pharmacokinetics, with protective antigen kinetics, during evaluation of the efficacy of raxibacumab in combination with ciprofloxacin for therapeutic treatment in the cynomolgus monkey inhalation anthrax model (Battelle Study No. 789-G923702)	Monkey Raxibacumab PK Ciprofloxacin PK	Randomized, placebo-controlled, double blind (GLP)	Placebo raxibacumab 40 mg/kg + ciprofloxacin 75 mg q12h x 6 ciprofloxacin gastric intubation raxibacumab IV *Treatment was administered based on detection of serum PA by individual animal	6 M, 6F (placebo) 7 M, 7 F (treatment groups)	Anthrax challenged	28 Days
PopPK	HGS1021-POP01.PK	Human raxibacumab pharmacokinetics and rabbit/monkey pa kinetic results for Protocol HGS1021-POP01	Human Pop PK Rabbit PA Kinetics Monkey PA Kinetics	NA	NA	322 Humans	Healthy and Anthrax challenged	NA
PD	PAM-NH01.PD	Pharmacodynamics results for Protocol PAM-NH-01	See above	See above	See above	See above	See above	See above

Type of Study	Study Identifier	Title of Report	Objective of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	Number (Sex) of Subjects per group	Healthy Subjects or Diagnosis of Patients	Duration of Study
PK	HGS1021-C1063.PK	Pharmacokinetic analysis of a randomized, single-blind, placebo-controlled study to evaluate the safety and tolerability of raxibacumab mAb (human monoclonal antibody to *B. anthracis* protective antigen) in healthy subjects	Ph 3 Human Raxibacumab PK	Randomized, single-blind, placebo-controlled	Raxibacumab or placebo (raxibacumab formulation buffer) single or double dose 40 mg/kg raxibacumab IV single dose on day 0 or double dose on days 0 and 14 Subjects were randomized 3:1 to treatment with raxibacumab or placebo in either the single or double dose group	165 M, 164 F 240 raxibacumab (217 single dose, 23 double dose) and 80 placebo (74 single dose, 6 double dose)	Healthy subjects	56 Days
PK	HGS1021-C1069.PK	Analysis of an open-label study to evaluate the immunogenicity and safety of raxibacumab (human monoclonal antibody to *B. anthracis* protective antigen) administered in healthy subjects	Ph 2/3 Human Raxibacumab PK	Open-label	Raxibacumab single dose 40 mg/kg raxibacumab IV Note: All subjects enrolled had received a single 40 mg/kg raxibacumab IV dose at least 4 months prior to receiving treatment in this study	12 M, 8 F	Healthy subjects	70 Days
Efficacy	290-N005433	Evaluation of the prophylactic efficacy of HGSI PA monoclonal antibody (PA mAb against aerosolized anthrax in the rabbit model	Monkey Pre-exposure prophylaxis Raxibacumab dose-ranging	Randomized, placebo-controlled (GLP)	Placebo (raxibacumab buffer), raxibacumab 10, 20, and 40 mg/kg SC *treatment was administered 2 days prior to anthrax challenge	5 M, 5 F	Anthrax challenged	28 Days (plus 60 days observati on period)
Efficacy	374-N006090 (This is a repeat challenge on surviving monkeys from 290-N005433)	Evaluation of the long term protective efficacy of PA mAb in the Cynomolgus monkey (Follow-up to 290-N005433)	Monkey rechallenge	Controlled (non-GLP)	No treatment intervention. Monkeys previously challenged with anthrax and treated with raxibacumab in Study 290-N05433.	11 M, 10 F	Anthrax challenged	28 Days
Efficacy	288-HGSIRAB	Evaluation of the prophylactic and therapeutic efficacy of HGSI PA monoclonal antibody (PA mAb) against aerosolized anthrax in the rabbit model	Rabbit Pre-exposure prophylaxis					
Efficacy	358-N005999	Evaluation of the therapeutic efficacy of HGSI PA monoclonal antibody (PA mAb) against aerosolized anthrax in the rabbit mode	Rabbit Pre/post exposure prophylaxis Raxibacumab time-ranging					
Efficacy	371-N006101	Post-exposure therapeutic intervention with PA mAb in the New Zealand white rabbit: Dose response study	Rabbit Pre/post exposure prophylaxis Raxibacumab dose-ranging	Randomized, placebo-controlled (GLP)	Placebo (raxibacumab buffer) or raxibacumab 5, 10, 20, and 40 mg/kg IV *treatment was initiated 24 hours or 36 hours (40 mg/kg group only) following spore challenge	6 M, 6 F	Anthrax challenged	14 Days
Model Characteriz ation	615-N104504	Exploratory study to evaluate markers of disease course of Bacillus anthracis in New Zealand white rabbits	Rabbit characterization	Natural history (non-GLP)	Not applicable (no treatment was administered)	4 M, 4 F	Anthrax challenged	7 Days
Model Characteriz ation	685-G005762	Natural history study to evaluate criteria for evidence of illness due to inhalation anthrax in Cynomolgus macaques	Monkey characterization	Natural history (non-GLP)	Not applicable (no treatment was administered)	7 M, 1 F	Anthrax challenged	30 Days

Type of Study	Study Identifier	Title of Report	Objective of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	Number (Sex) of Subjects per group	Healthy Subjects or Diagnosis of Patients	Duration of Study
Efficacy	682-G005758	Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the rabbit model	Rabbit efficacy	Randomized, placebo-controlled (GLP)	Placebo (raxibacumab buffer) or raxibacumab 20 and 40 mg/kg IV *Treatment was administered based on detection of increased temperature or serum PA by individual animal	9 M, 9 F	Anthrax challenged	14 Days
Histology	EPL 866-001 to accompany682-G005758	Blinded re-read of selected slides and tissues from the study" Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the rabbit model"	Histology	GLP	See above	See above	See above	See above
Efficacy	724-G005829	Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the cynomolgus macaque	Monkey efficacy	Randomized, double-blind, placebo-controlled (GLP)	Placebo (raxibacumab buffer) or raxibacumab 20 and 40 mg/kg IV *Treatment was administered based on detection of serum PA by individual animal	12 M, 12 F (placebo) 14 M, 14 F (treatment groups)	Anthrax challenged	28 Days
Histology	901-G005829 to accompany 724-G005829	Assessing the terminal pathology of cynomolgus macaques aerosol challenged with bacillus anthracis and treated with raxibacumab or placebo	Histology	GLP	See above	See above	See above	See above
Histology	EPL 866-002 to accompany 724-G005829	Blinded re-read of selected slides and tissues from the study "Evaluation of raxibacumab efficacy as therapeutic treatment against inhalation anthrax in the cynomolgus macaque"	Histology	GLP	See above	See above	See above	See above
Efficacy and PK	723-G005835	Levofloxacin pharmacokinetics and protective antigen kinetics during a pilot study evaluation of levofloxacin efficacy as therapeutic treatment against inhalation anthrax in the rabbit model (Battelle Study No. 723-G005835)	Rabbit Levofloxacin Therapeutic efficacy and PK	Pilot, placebo controlled (non-GLP)	Levofloxacin 10, 25, and 50 mg/mL once daily x 3 gastric intubation/oral gavage or untreated control *Treatment was administered based on detection of increased temperature by individual animal	4 M, 4 F (+3 M control)	Anthrax challenged	21 Days
Efficacy	781-G923701	Evaluating the Efficacy of Raxibacumab in Combination with Levofloxacin for Post-exposure Treatment in the New Zealand White Rabbit Inhalational Anthrax Model	Rabbit Raxibacumab / levofloxacin Therapeutic efficacy	Randomized, double-blind, placebo-controlled (GLP)	Placebo (raxibacumab buffer) 50 mg/mL levofloxacin PO doses q12h x 6 50 mg/mL levofloxacin PO doses q12h x 6 + 40 mg/kg raxibacumab *Treatment was administered based on detection of increased temperature or serum PA by individual animal	12 M, 12 F (placebo) 20 M, 20 F (treatment groups)	Anthrax challenged	28 Days
Efficacy	789-G923702	Evaluation of the Efficacy of Raxibacumab in Combination with Ciprofloxacin for Therapeutic Treatment in the Cynomolgus Monkey Inhalation Anthrax Model (Battelle Study 789-G923702)	Monkey Raxibacumab / ciprofloxacin combination study	Randomized, double-blind, placebo-controlled (GLP)	Placebo (raxibacumab buffer) 75 mg/ ciprofloxacin PO doses q12h x 6 75 mg ciprofloxacin PO doses q12h x 6 + 40 mg/kg raxibacumab *Treatment was administered based	12 M, 12 F (placebo) 14 M, 14 F (treatment groups)	Anthrax challenged	28 Days

Type of Study	Study Identifier	Title of Report	Objective of the Study	Study Design and Type of Control	Test Product(s): Dosage Regimen: Route of Administration	Number (Sex) of Subjects per group	Healthy Subjects or Diagnosis of Patients	Duration of Study
					on detection of serum PA by individual animal			
Safety	PAM-NH-01.CSR	A phase 1 single-blind, placebo-controlled, single-injection, dose escalation study to evaluate the safety and pharmacokinetics of PA mAb (human monoclonal antibody to B. anthracis protective antigen) in healthy subjects	Ph 1 human safety and PK	Single-blind, dose-escalation, placebo controlled (non-GLP1)	Raxibacumab or placebo (raxibacumab formulation buffer) single dose 0.3, 1, and 3 mg/kg IM (gluteus maximus) 1 and 3 mg/kg IM (vastus lateralis) 1, 3, 10, 20, and 40 mg/kg IV	80 raxibacumab, 25 placebo	Healthy subjects	56 Days
Immuno-genicity	PAM-NH-01.IM	Immunogenicity Results for Protocol PAM-NH-01	Ph 1 human	Single-blind, dose-escalation, placebo controlled (non-GLP1)	Raxibacumab or placebo (raxibacumab formulation buffer) single dose 0.3, 1, and 3 mg/kg IM (gluteus maximus) 1 and 3 mg/kg IM (vastus lateralis) 1, 3, 10, 20, and 40 mg/kg IV	80 raxibacumab, 25 placebo	Healthy subjects	56 Days
Safety	HGS1021-C1063.CSR	A randomized, single-blind, placebo-controlled study to evaluate the safety and tolerability of raxibacumab mAb (human monoclonal antibody to B. anthracis protective antigen) in healthy subjects	Human safety	Randomized, single-blind, placebo-controlled (non-GLP1)	Raxibacumab or placebo (raxibacumab formulation buffer) single or double dose 40 mg/kg raxibacumab IV single dose on day 0 or double dose on days 0 and 14	165 M, 164 F 240 raxibacumab (217 single dose, 23 double dose) and 80 placebo (74 single dose, 6 double dose)	Healthy subjects	56 Days after last dose
Safety	HGS1021-C1064.CSR	An open-label study to evaluate the pharmacokinetics and safety of raxibacumab (human monoclonal antibody to B. anthracis protective antigen) administered in combination with ciprofloxacin in healthy subjects	Safety and PK of raxibacumab in combination with ciprofloxacin	Randomized (Groups 1 & 2), open-label (non-GLP1)	Raxibacumab single dose and/or ciprofloxacin for 7.5 days 500 mg ciprofloxacin PO doses q12h x 15 doses on days 0-7 + 40 mg/kg raxibacumab IV on day 5 (Group 1) 40 mg/kg raxibacumab IV on day 0 (Group 2) 400 mg ciprofloxacin IV q12h x 2 doses + 40 mg/kg raxibacumab IV on day 0 and 500 mg ciprofloxacin PO q12h x 13 doses on days 1-7	43 M, 45 F	Healthy subjects	56 Days
Safety	HGS1021-C1069.CSR	An open-label study to evaluate the immunogenicity and safety of raxibacumab (human monoclonal antibody to B. anthracis protective antigen) administered in healthy subjects	Safety of raxibacumab reinjection after wash-out	Open-label (non-GLP1)	Raxibacumab single dose 40 mg/kg raxibacumab IV Note: All subjects enrolled had received a single 40 mg/kg raxibacumab IV dose at least 4 months prior to receiving treatment in this study	12 M, 8 F	Healthy subjects	70 Days